CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

ANDA 76-250

***Name*:** Niacin Extended-release Tablets, 1000 mg

***Sponsor*:** Barr Laboratories, Inc.

***Approval Date*:** April 14, 2005

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 76-250

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APPLICATION NUMBER:

ANDA 76-250

APPROVAL LETTER

ANDA 76-250

Barr Laboratories, Inc.
Attention: Nicholas Tantillo
2 Quaker Road
P.O. Box 2900
Pomona, NY 10970

APR 14 2005

Dear Sir:

This is in reference to your abbreviated new drug application (ANDA) dated October 2, 2001, submitted pursuant to section 505(j) of the Federal Food, Drug, and Cosmetic Act (the Act), for Niacin Extended-release Tablets, 1000 mg.

Reference is also made to the Tentative Approval letter issued by this office on May 9, 2003, and to your amendments dated May 17, 2002; and January 28, March 4, and March 11, 2005.

We have completed the review of this abbreviated application and have concluded that the drug is safe and effective for use as recommended in the submitted labeling. Accordingly, the application is approved. The Division of Bioequivalence has determined your Niacin Extended-release Tablets, 1000 mg to be bioequivalent and, therefore, therapeutically equivalent to the listed drug Niaspan® Tablets of KOS Pharmaceuticals, Inc.

Your dissolution testing should be incorporated into the stability and quality control program using the same method proposed in your application. The "interim" dissolution specifications are as follows:

The dissolution testing should be conducted in 900 mL of water at 37°C, using USP Apparatus I (basket) at 100 rpm. The test product should meet the following "interim" dissolution specifications:

Time (hours)	Percent Dissolved
1	
3	
6	
9	
12	
20	

The "interim" dissolution tests and tolerances should be finalized by submitting dissolution data for the first three production size batches. Data should be submitted as a Special Supplement - Changes Being Effected when there are no revisions to the "interim" specifications or when the final specifications are tighter than the "interim" specifications. In all other instances, the information should be submitted in the form of a Prior Approval Supplement.

The referenced listed drug product (RLD) upon which you have based your application, Niaspan® Tablets of KOS Pharmaceuticals, Inc. (KOS), is subject to multiple periods of patent protection. The following U.S. patents with their expiration dates are currently listed in the Agency's publication entitled Approved Drug Products with Therapeutic Equivalence Evaluations (the "Orange Book"):

Patent Number	Expiration Date
6,080,428 (the '428)	May 27, 2017
6,129,930 (the '930)	September 20, 2013
6,406,715 (the '715)	October 31, 2017
6,676,967 (the '967)	September 20, 2013
6,746,691 (the '691)	September 20, 2013
6,818,229 (the '229)	February 15, 2014

Your application contains paragraph IV certifications to each of these patents under section 505(j)(2)(A)(vii)(IV) of the Act stating that the claims of these patents are invalid, unenforceable, or will not be infringed by your manufacture, use, or sale of the Niacin Extended-release Tablets, 1000 mg, under this ANDA. You further informed the Agency that KOS initiated a patent infringement suit against you in the United States District Court for the Southern District of New York (KOS Pharmaceuticals v. Barr Laboratories, Inc., [KOS III] Consolidated Civil Action No. 02-CV-1683) to the '428, '930, and '715 patents. The Agency also recognizes that the 30-month period identified in section 505(j)(5)(B)(iii) of the Act, during which time FDA was precluded from approving your application, expired on March 30, 2005, with respect to these three patents. You have notified the Agency that no action for patent infringement involving the '691 patent was brought against Barr Laboratories, Inc. (Barr) within the statutory 45-day period, and that no action for patent infringement involving the '229 patent was brought against Barr. Furthermore, we note that although KOS initiated litigation against Barr for

infringement of the '967 patent [Civil Action No. 04-CV-2403], the '967 patent information was submitted to FDA on February 11, 2004, which is both after the applicable August 18, 2003 effective date of the MMA and after the date of submission of your ANDA. Therefore, there could be no 30-month stay under section 505(j)(5)(B)(iii)[1] with respect to your paragraph IV certification to the '967 patent. See MMA § 1101(c)(3).

With regard to 180-day generic drug exclusivity and Niacin Extended-release Tablets, 1000 mg, Barr was the first ANDA applicant to submit a substantially complete ANDA with a paragraph IV certification to the patents listed above. Therefore, Barr is eligible for 180 days of market exclusivity for Niacin Extended-release Tablets, 1000 mg. This exclusivity, which is provided for under section 505(j)(5)(B)(iv) of the Act,[2] will begin to run from the earlier of the commercial marketing or court decision dates identified in section 505(j)(5)(B)(iv). Please submit correspondence to this application informing the Agency of the date the exclusivity begins to run.

Under section 506A of the Act, certain changes in the conditions described in this ANDA require an approved supplemental application before the change may be made.

Post-marketing reporting requirements for this ANDA are set forth in 21 CFR 314.80-81 and 314.98. The Office of Generic Drugs should be advised of any change in the marketing status of this drug.

Promotional materials may be submitted to FDA for comment prior to publication or dissemination. Please note that these submissions are voluntary. If you desire comments on proposed launch promotional materials with respect to compliance with applicable regulatory requirements, we recommend you submit, in draft or mock-up form, two copies of both the promotional materials and package insert(s) directly to:

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1 Because information on the '428, '930, and '715 patents was submitted to FDA before August 18, 2003, references to section 505(j)(5)(B)(iii) with respect to those patents are to that section of the Act as in effect prior to December 8, 2003, when the Medicare Prescription Drug, Improvement and Modernization Act (MMA)(Public Law 108-173) was enacted. However, information on the '967, '691, and '229 patents was submitted to FDA after submission of your ANDA and after August 18, 2003, so references to section 505(j)(5)(B)(iii) with respect to those patents are to that section of the Act as in effect after December 8, 2003. See MMA § 1101(c)(3).

2 Because your ANDA was filed before the date of enactment of the MMA on December 8, 2003, this reference to the 180-day exclusivity provision is to the section of the Act as in effect prior to December 8, 2003. See MMA § 1102(b)(1).

Food and Drug Administration
Division of Drug Marketing, Advertising, and Communications, HFD-42
5600 Fishers Lane
Rockville, MD 20857

We call your attention to 21 CFR 314.81(b)(3) which requires that materials for any subsequent advertising or promotional campaign be submitted to our Division of Drug Marketing, Advertising, and Communications (HFD-40) with a completed Form FDA 2253 at the time of their initial use.

Sincerely yours,

Gary Buehler 4/14/05
Director
Office of Generic Drugs
Center for Drug Evaluation and Research

cc: ANDA 76-250
Division File
Field Copy
HFD-610/R. West
HFD-205
HFD-610/Orange Book Staff
HFD-600/C. Parise
HFD-604/D. Hare

Approved Electronic Labeling Located at:
\\cdsesubogd1\n76250\N_000\2005-01-28\labeling\pi.pdf

Endorsements:

HFD-625/B.Cai/ 4/12/05
HFD-623/A.Mueller/ 4-12-05
HFD-617/B.Danso/ 4/12/05
HFD-613/A.Payne/
HFD- 613/J.Grace/

4/14/05
Bob West

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F/T by:

APPROVAL
PACT

4/12/05

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 76-250

TENTATIVE APPROVAL LETTER

ANDA 76-250

MAY 9 2003

Barr Laboratories, Inc.
Attention: Nicholas Tantillo
2 Quaker Road
P.O. Box 2900
Pomona, NY 10970-0519

Dear Sir:

This is in reference to your abbreviated new drug application (ANDA) dated October 2, 2001, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act (Act), for Niacin Extended-release Tablets, 1000mg.

Reference is also made to your amendments dated May 17 and December 13, 2002, and February 24, 2003. We acknowledge receipt of your correspondence dated March 4, March 22, August 29, August 30, and December 9, 2002, pertaining to the patent and litigation issues noted below.

We have completed the review of this abbreviated application, and based upon the information you have presented to date, we have concluded that the drug is safe and effective for use as recommended in the submitted labeling. Although we are unable to grant final approval at this time due patent protection granted to the NDA holder, your application is **tentatively approved**. This tentative approval is based upon information available to the agency at this time (i.e., information in your application and the status of current good manufacturing practices (cGMPs) of the facilities used in the manufacture and testing of the drug product). This determination is subject to change on the basis of new information that may come to our attention. This letter does not address notice issues related to the 180-day exclusivity provisions under section 505(j)(5)(B)(iv) of the Act.

The reference listed drug product (RLD) upon which you have based your application, Niaspan® Tablets of KOS Pharmaceuticals, Inc., is subject to periods of patent protection. As noted in the agency's publication entitled Approved Drug Products with Therapeutic Equivalence Evaluations, the "Orange Book", U.S.

patent 6,080,428 (the '428 patent), U.S. patent 6,129,930 (the '930 patent), and U.S. patent 6,406,715 (the '715 patent) are scheduled to expire on May 27, 2017, September 20, 2013, and October 31, 2017 respectively. Your application contains paragraph IV certifications to each of these patents under Section 505(j)(2)(A)(vii)(IV) of the act stating that these patents are invalid, unenforceable, or will not be infringed by your manufacture, use, or sale of Niacin Extended-release Tablets under this ANDA. Section 505(j)(5)(B)(iii) of the act provides that approval of an ANDA may be made effective immediately, unless an action is brought against Barr prior to the expiration of 45 days from the date the notice you provided under paragraph (2)(B)(i) was received by the NDA/patent holder.

You have notified the agency that Barr complied with the requirements of section 505(j)(2)(B) of the act. As a result, Barr was sued for patent infringement in the United States District Court for the Southern District of New York involving a challenge to each of the three patents (KOS Pharmaceuticals, Inc., v. Barr Laboratories, Inc., Civil Action No. 02-CV-8995 and 02-CV-1683). Therefore, final approval cannot be granted until:

1. a. the expiration of the 30-month periods provided for in section 505(j)(5)(B)(iii) since the date of receipt of the 45-day notices required under section 505(j)(2)(B)(i), unless the court has extended or reduced the periods because of the failure of either party to reasonably cooperate in expediting the actions, or,

   b. the date of court decision [505(j)(5)(B)(iii)(I), (II), or (III)], or,

   c. the '428, '930, and '715 patents have expired, and

2. The agency is assured there is no new information that would affect whether final approval should be granted.

In order to reactivate your application prior to final approval, please submit a MINOR AMENDMENT - FINAL APPROVAL REQUESTED between 60 to 90 days prior to the date you believe that your application will be eligible for final approval. This amendment should provide:

1. A copy of a final order or judgement from the district court, or a settlement agreement or a licensing agreement between you and the patent holder, or any other relevant information, and

2. a. updated information related to final-printed labeling or chemistry, manufacturing and controls data, or any other change in the conditions outlined in this abbreviated application, or

   b. a statement that no such changes have been made to the application since the date of tentative approval.

In addition to the minor amendment requested above, the agency may request at any time prior to the final date of approval request that you submit an additional amendment containing the requested information. Failure to submit either or, if requested, both amendments may result in rescission of the tentative approval status of your application, or may result in a delay in issuance of the final approval letter.

Any significant changes in the conditions outlined in this abbreviated application as well as changes to the status of the manufacturing and testing facilities' compliance with current good manufacturing practices (cGMPs) are subject to agency review before final approval of the application will be made. Such changes should be submitted as an amendment to the application and categorized as representing either "major" or "minor" changes. The amendment will be reviewed according to OGD policy in effect at the time of receipt. Your submission of multiple amendments prior to final approval may lead to a delay in the issuance of the final approval letter.

This drug product may not be marketed without final agency approval under section 505 of the Act. The introduction or delivery for introduction into interstate commerce of this drug before the final approval date is prohibited under section 501 of the Act and 21 U.S.C. 331(d). Also, until the agency issues the final approval letter, this drug product will not be deemed approved for marketing under 21 U.S.C. 355, and it will not be listed in the "Orange Book."

For further information on the status of this application, or prior to submitting additional amendments, please contact Wanda Pamphile, Pharm.D., Project Manager, at 301-827-5763.

Sincerely yours,

Robert Lu Sett 1 for
5/9/2003

Gary Buehler
Director
Office of Generic Drugs
Center for Drug Evaluation and Research

APPEARS THIS WAY
ON ORIGINAL

cc: ANDA 76-250
Division File
Field Copy
HFD-610/R. West
HFD-330
HFD-205
HFD-610/Orange Book Staff

Endorsements:
HFD-625/B.Cai/ 4/23/03
HFD-625/S.Liu/ S.H. Liu 4/23/03
HFD-617/W.~~Pamphile~~ Pamphile/ for 4/23/03
HFD-613/A.Payne/ 4/29/03
HFD-613/J.Grace/ 4/29/2003

Robert West 5/9/2003

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F/T by:ard/3/23/03

TENTATIVE APPROVAL

5/1/03

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 76-250

LABELING

NIACIN EXTENDED-RELEASE TABLETS

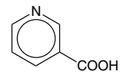
Revised JANUARY 2005
1002140101

Rx only

BARR LABORATORIES, INC.

DESCRIPTION:

Niacin Extended-Release Tablets contain niacin, a B-complex vitamin and antihyperlipidemic agent. Niacin (nicotinic acid, or 3-pyridinecarboxylic acid) is a white, crystalline powder, very soluble in water, with the following structural formula:



$C_6H_5NO_2$ Molecular Weight: 123.11

Niacin Extended-Release Tablets, for oral administration, does not contain any color additives and is available in the strength containing 1000 mg niacin. Niacin Extended-Release Tablets also contain the following inactive ingredients: hypromellose, povidone, and stearic acid.

CLINICAL PHARMACOLOGY:

Niacin functions in the body after conversion to nicotinamide adenine dinucleotide (NAD) in the NAD coenzyme system. Niacin (but not nicotinamide) in gram doses reduces total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C) and triglycerides (TG), and increases high-density lipoprotein cholesterol (HDL-C). The magnitude of individual lipid and lipoprotein responses may be influenced by the severity and type of underlying lipid abnormality. The increase in total HDL-C is associated with an increase in apolipoprotein A-I (Apo A-I) and a shift in the distribution of HDL subfractions. These shifts include an increase in the HDL_2:HDL_3 ratio, and an elevation in lipoprotein A-I (Lp A-I, an HDL particle containing only Apo A-I). Niacin treatment also decreases serum levels of apolipoprotein B-100 (Apo B), the major protein component of the very low-density lipoprotein (VLDL) and LDL fractions, and of Lp(a), a variant form of LDL independently associated with coronary risk.[1] In addition, preliminary reports suggest that niacin causes favorable LDL particle size transformations, although the clinical relevance of this effect requires further investigation. The effect of niacin-induced changes in lipids/lipoproteins on cardiovascular morbidity or mortality in individuals without pre-existing coronary disease has not been established.

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

Like LDL, cholesterol-enriched triglyceride-rich lipoproteins, including VLDL, intermediate-density lipoprotein (IDL), and remnants, can also promote atherosclerosis. Elevated plasma TG are frequently found in a triad with low HDL-C levels and small LDL particles, as well as in association with non-lipid metabolic risk factors for coronary heart disease (CHD). As such total plasma TG has not consistently been shown to be an independent risk factor for CHD. Furthermore, the independent effect of raising HDL-C or lowering TG on the risk of coronary and cardiovascular morbidity and mortality has not been determined.

Mechanism of Action:

The mechanism by which niacin alters lipid profiles has not been well defined. It may involve several actions including partial inhibition of release of free fatty acids from adipose tissue, and increased lipoprotein lipase activity, which may increase the rate of chylomicron triglyceride removal from plasma. Niacin decreases the rate of hepatic synthesis of VLDL and LDL, and does not appear to affect fecal excretion of fats, sterols, or bile acids.

Pharmacokinetics/Metabolism:

Absorption: Niacin is rapidly and extensively absorbed (at least 60 to 76% of dose) when administered orally. To maximize bioavailability and reduce the risk of gastrointestinal (GI) upset, administration of niacin extended-release tablets with a low-fat meal or snack is recommended.

Single-dose bioavailability studies have demonstrated that niacin extended-release tablet strengths are not interchangeable.

Distribution: Studies using radiolabeled niacin in mice show that niacin and its metabolites concentrate in the liver, kidney and adipose tissue.

Metabolism: The pharmacokinetic profile of niacin is complicated due to rapid and extensive first-pass metabolism, which is species and dose-rate specific. In humans, one pathway is through a simple conjugation step with glycine to form nicotinuric acid (NUA). NUA is then excreted in the urine, although there may be a small amount of reversible metabolism back to niacin. The other pathway results in the formation of nicotinamide adenine dinucleotide (NAD). It is unclear whether nicotinamide is formed as a precursor to, or following the synthesis of, NAD. Nicotinamide is further metabolized to at least N-methylnicotinamide (MNA) and nicotinamide-N-oxide (NNO). MNA is further metabolized to two other compounds, N-methyl-2-pyridone-5-carboxamide (2PY) and N-methyl-4-pyridone-5-carboxamide (4PY). The formation of 2PY appears to predominate over 4PY in humans. At the doses used to treat hyperlipidemia, these metabolic pathways are saturable, which explains the nonlinear relationship between niacin dose and plasma concentrations following multiple-dose niacin extended-release tablets administration (Table 1).

Nicotinamide does not have hypolipidemic activity; the activity of the other metabolites is unknown.

Table 1. Mean Steady-State Pharmacokinetic Parameters for Plasma Niacin

Niacin Extended-Release Tablets		Niacin	
dose/day	given as	Peak Concentration (µg/mL)	Time to Peak (hrs)
1000 mg	2 x 500 mg	0.6	5
1500 mg	2 x 750 mg	4.9	4
2000 mg	2 x 1000 mg	15.5	5

Elimination: Niacin and its metabolites are rapidly eliminated in the urine. Following single and multiple doses, approximately 60 to 76% of the niacin dose administered as niacin extended-release tablets was recovered in urine as niacin and metabolites; up to 12% was recovered as unchanged niacin after multiple dosing. The ratio of metabolites recovered in the urine was dependent on the dose administered.

Special Populations: Hepatic: No studies have been performed. Niacin extended-release tablets should be used with caution in patients with a past history of liver disease, who consume substantial quantities of alcohol, or have unexplained transaminase elevations. Niacin extended-release tablets are contraindicated in patients with active liver disease (see WARNINGS).

Renal: There are no data in this population. Niacin extended-release tablets should be used with caution in patients with renal disease (see PRECAUTIONS).

Gender: Steady-state plasma concentrations of niacin and metabolites after administration of niacin extended-release tablets are generally higher in women than in men, with the magnitude of the difference varying with dose and metabolite. Recovery of niacin and metabolites in urine, however, is generally similar for men and women, indicating that absorption is similar for both genders. The gender differences observed in plasma levels of niacin and its metabolites may be due to gender-specific differences in metabolic rate or volume of distribution. Data from the clinical trials suggest that women have a greater hypolipidemic response than men at equivalent doses of niacin extended-release tablets.

Niacin Clinical Studies:

The role of LDL-C in atherogenesis is supported by pathological observations, clinical studies, and many animal experiments. Observational epidemiological studies have clearly established that high TC or LDL-C and low HDL-C are risk factors for CHD. Additionally, elevated levels of Lp(a) have been shown to be independently associated with CHD risk.[1] The efficacy of niacin in improving lipoprotein lipid profiles, either alone or in combination with other lipid-altering drugs, as an adjunct to diet therapy in the treatment of hyperlipoproteinemia has been well documented.

Niacin's ability to reduce mortality and the risk of definite, nonfatal myocardial infarction (MI) has also been assessed in long-term studies. The Coronary Drug Project,[2] completed in 1975, was designed to assess the safety and efficacy of niacin and other lipid-altering drugs in men 30 to 64 years old with a history of MI. Over an observation period of 5 years, niacin treatment was associated with a statistically significant reduction in nonfatal, recurrent MI. The incidence of definite, nonfatal MI was 8.9% for the 1,119 patients randomized to nicotinic acid versus 12.2% for the 2,789 patients who received placebo (p<0.004). Total mortality was similar in the two groups at 5 years (24.4% with nicotinic acid versus 25.4% with placebo; p=N.S.). At the time of a 15-year follow-up, there were 11% (69) fewer deaths in the niacin group compared to the placebo cohort (52.0% versus 58.2%; p=0.0004).[3] However, mortality at 15 years was not an original endpoint of the Coronary Drug Project. In addition, patients had not received niacin for approximately 9 years, and confounding variables such as concomitant medication use and medical or surgical treatments were not controlled.

The Cholesterol-Lowering Atherosclerosis Study (CLAS) was a randomized, placebo-controlled, angiographic trial testing combined colestipol and niacin therapy in 162 non-smoking males with previous coronary bypass surgery.[4] The primary, per-subject cardiac endpoint was global coronary artery change score. After 2 years, 61% of patients in the placebo cohort showed disease progression by global change score (n=82), compared with only 38.8% of drug-treated subjects (n=80), when both native arteries and grafts were considered (p<0.005); disease regression also occurred more frequently in the drug-treated group (16.2% versus 2.4%; p=0.002). In a follow-up to this trial in a subgroup of 103 patients treated for 4 years, again, significantly fewer patients in the drug-treated group demonstrated progression than in the placebo cohort (48% versus 85%, respectively; p<0.0001).[5]

The Familial Atherosclerosis Treatment Study (FATS) in 146 men ages 62 and younger with Apo B levels ≥125 mg/dL, established coronary artery disease, and family histories of vascular disease, assessed change in severity of disease in the proximal coronary arteries by quantitative arteriography.[6] Patients were given dietary counseling and randomized to treatment with either conventional therapy with double placebo (or placebo plus colestipol if the LDL-C was elevated); lovastatin plus colestipol; or niacin plus colestipol. In the conventional therapy group, 46% of patients had disease progression (and no regression) in at least one of nine proximal coronary segments; regression was the only change in 11%. In contrast, progression (as the only change) was seen in only 25% in the niacin plus colestipol group, while regression was observed in 39%. Though not an original endpoint of the trial, clinical events (death, MI, or revascularization for worsening angina) occurred in 10 of 52 patients who received conventional therapy, compared with 2 of 48 who received niacin plus colestipol.

The Harvard Atherosclerosis Reversibility Project (HARP) was a randomized placebo-controlled, 2.5-year study of the effect of a stepped-care antihyperlipidemic drug regimen on 91 patients (80 men and 11 women) with CHD and average baseline TC levels less than 250 mg/dL and ratios of TC to HDL-C greater than 4.0.[7] Drug treatment consisted of an HMG-CoA reductase inhibitor administered alone as initial therapy followed by addition of varying dosages of either a slow-release nicotinic acid, cholestyramine, or gemfibrozil. Addition of nicotinic acid to the HMG-CoA reductase inhibitor resulted in further statistically significant mean reductions in TC, LDL-C, and TG, as well as a further increase in HDL-C in a majority of patients (40 of 44 patients). The ratios of TC to HDL-C and LDL-C to HDL-C were also significantly reduced by this combination drug regimen (see WARNINGS, Skeletal Muscle).

Niacin Extended-Release Tablets Clinical Studies:

Placebo-Controlled Clinical Studies in Patients with Primary Hypercholesterolemia and Mixed Dyslipidemia: In two randomized, double-blind, parallel, multi-center, placebo-controlled trials, niacin extended-release tablets dosed at 1000, 1500 or 2000 mg daily at bedtime with a low-fat snack for 16 weeks (including 4 weeks of dose escalation) favorably altered lipid profiles compared to placebo (Table 2). Women appeared to have a greater response than men at each niacin extended-release tablet dose level (see Gender Effect, below).

Table 2. Lipid Response to Niacin Extended-Release Tablets Therapy

		Mean Percent Change from Baseline to Week 16*							
Treatment	n	TC	LDL-C	HDL-C	TC/HDL-C	TG	Lp (a)	Apo B	Apo A-1
Niacin Extended-Release Tablets 1000 mg qhs	41	-3	-5	+18	-17	-21	-13	-6	+9
Niacin Extended-Release Tablets 2000 mg qhs	41	-10	-14	+22	-25	-28	-27	-16	+8
Placebo	40	0	-1	+4	-3	0	0	+1	+3
Niacin Extended-Release Tablets 1500 mg qhs	76	-8	-12	+20	-20	-13	-15	-12	+8
Placebo	73	+2	+1	+2	+1	+12	+2	+1	+2

n = number of patients at baseline;

* Mean percent change from baseline for all niacin extended-release tablets doses was significantly different (p<0.05) from placebo for all lipid parameters shown except Apo A-1 at 2000 mg.

In a double-blind, multi-center, forced dose-escalation study, monthly 500 mg increases in niacin extended-release tablets dose resulted in incremental reductions of approximately 5% in LDL-C and Apo B levels in the daily dose range of 500 mg through 2000 mg (Table 3). Women again tended to have a greater response to niacin extended-release tablets than men (see Gender Effect, below).

Table 3. Lipid Response in Dose-Escalation Study

		Mean Percent Change from Baseline*							
Treatment	n	TC	LDL-C	HDL-C	TC/HDL-C	TG	Lp (a)	Apo B	Apo A-1
Placebo‡	44	-2	-1	+5	-7	-6	-5	-2	+4
Niacin Extended-Release Tablets 500 mg qhs	87	-2	-3	+10	-10	-5	-3	-2	+5
1000 mg qhs		-5	-9	+15	-17	-11	-12	-7	+8
1500 mg qhs		-11	-14	+22	-26	-28	-20	-15	+10
2000 mg qhs		-12	-17	+26	-29	-35	-24	-16	+12

n = number of patients enrolled;

‡ Placebo data shown are after 24 weeks of placebo treatment.

* For all niacin extended-release tablets doses except 500 mg, mean percent change from baseline was significantly different (p<0.05) from placebo for all lipid parameters shown except Lp(a) and Apo A-1 which were significantly different from placebo starting with 1500 mg and 2000 mg, respectively.

Pooled results for major lipids from these three placebo-controlled studies are shown below (Table 4).

Table 4. Selected Lipid Response to Niacin Extended-Release Tablets in Placebo-Controlled Clinical Studies*

		Mean Baseline and Median Percent Change from Baseline (25th, 75th Percentiles)		
Niacin Extended-Release Tablets Dose	n	LDL-C	HDL-C	TG
1000 mg qhs	104			
Baseline (mg/dL)		218	45	172
Percent Change		-7 (-15, 0)	+14 (+7, +23)	-16 (-34, +3)
1500 mg qhs	120			
Baseline (mg/dL)		212	46	171
Percent Change		-13 (-21, -4)	+19 (+9, +31)	-25 (-45, -2)
2000 mg qhs	85			
Baseline (mg/dL)		220	44	160
Percent Change		-16 (-26, -7)	+22 (+15, +34)	-38 (-52, -14)

* Represents pooled analyses of results; minimum duration on therapy at each dose was 4 weeks.

Gender Effect: Combined data from the three placebo-controlled niacin extended-release tablets studies in patients with primary hypercholesterolemia and mixed dyslipidemia suggest that, at each niacin extended-release tablets dose level studied, changes in lipid concentrations are greater for women than for men (Table 5).

Table 5. Effect of Gender on Niacin Extended-Release Tablets Dose Response

		Mean Percent Change from Baseline							
	n	LDL-C		HDL-C		TG		Apo B	
Niacin Extended-Release Tablets Dose	(M/F)	M	F	M	F	M	F	M	F
500 mg qhs	50/37	-2	-5	+11	+8	-3	-9	-1	-5
1000 mg qhs	76/52	-6*	-11*	+14	+20	-10	-20	-5*	-10*
1500 mg qhs	104/59	-12	-16	+19	+24	-17	-28	-13	-15
2000 mg qhs	75/53	-15	-18	+23	+26	-30	-36	-16	-16

n = Number of male/female patients enrolled.

* Percent change significantly different between genders (p<0.05).

Other Patient Populations: In a double-blind, multi-center, 19-week study the lipid-altering effects of niacin extended-release tablets (forced titration to 2000 mg qhs) were compared to baseline in patients whose primary lipid abnormality was a low level of HDL-C (HDL-C≤40 mg/dL, TG ≤400 mg/dL, and LDL-C≤160, or <130 mg/dL in the presence of CHD). Results are shown below (Table 6).

Table 6. Lipid Response to Niacin Extended-Release Tablets in Patients with Low HDL-C

		Mean Baseline and Mean Percent Change from Baseline								
	n	TC	LDL- C	HDL- C	TC/HDL-C	TG	Lp (a)†	Apo B†	Apo A-I†	Lp A-I†
Baseline (mg/dL)	88	190	120	31	6	194	8	106	105	32
Week 19 (% Change)	71	-3	0	+26	-22	-30	-20	-9	+11	+20

n = number of patients

* Mean percent change from baseline was significantly different (p<0.05) for all lipid parameters shown except LDL-C.

† n = 72 at baseline and 69 at week 19.

‡ n = 30 at baseline and week 19.

At niacin extended-release tablets 2000 mg/day, median changes from baseline (25th, 75th percentiles) for LDL-C, HDL-C, and TG were -3% (-14, +12%), +27% (+13, +38%), and -33% (-50, -19%), respectively.

Combination Niacin Extended-Release Tablets and Lovastatin Study: In a multi-center, randomized, double-blind, parallel, 28-week study, a combination tablet of niacin extended-release tablets and lovastatin was compared to each individual component in patients with Type IIa and IIb hyperlipidemia. Using a forced dose-escalation study design, patients received each dose for at least 4 weeks. Patients randomized to treatment with the combination tablet of niacin extended-release tablets and lovastatin initially received 500 mg/20 mg (expressed as mg of niacin/mg of lovastatin) once daily before bedtime. The dose was increased by 500 mg at 4-week intervals (based on the niacin extended-release tablets component) to a maximum dose of 1000 mg/20 mg in one-half of the patients and 2000 mg/40 mg in the other half. The niacin extended-release tablets monotherapy group underwent a similar titration from 500 mg to 2000 mg. The patients randomized to lovastatin monotherapy received 20 mg for 12 weeks titrated to 40 mg for up to 16 weeks. Up to a third of the patients randomized to the combination tablet of niacin extended-release tablets and lovastatin or niacin extended-release tablets monotherapy discontinued prior to Week 28. Results from this study showed that combination therapy decreased LDL-C, TG and Lp(a), and increased HDL-C in a dose-dependent fashion (Tables 7, 8, 9, and 10). Results from this study for LDL-C mean percent change from baseline (the primary efficacy variable) showed that:

1) LDL-lowering with the combination tablet of niacin extended-release tablets and lovastatin was significantly greater than that achieved with lovastatin 40 mg only after 28 weeks of titration to a dose of 2000 mg/40 mg (p<0.0001)

2) The combination tablet of niacin extended-release tablets and lovastatin at doses of 1000 mg/20 mg or higher achieved greater LDL-lowering than niacin extended-release tablets (p<0.0001)

The LDL-C results are summarized in Table 7.

Table 7. LDL-C Mean Percent Change From Baseline

Week	Combination Tablet of Niacin Extended-Release Tablets and Lovastatin			Niacin Extended-Release Tablets			Lovastatin		
	n*	Dose (mg/mg)	LDL	n*	Dose (mg)	LDL	n*	Dose (mg)	LDL
Baseline	57	-	190.9 mg/dL	61	-	189.7 mg/dL	61	-	185.6 mg/dL
12	47	1000/20	-30%	46	1000	-3%	56	20	-29%
16	45	1000/40	-36%	44	1000	-6%	56	40	-31%
20	42	1500/40	-37%	43	1500	-12%	54	40	-34%
28	42	2000/40	-42%	41	2000	-14%	53	40	-32%

* n = number of patients remaining in trial at each time point

Combination therapy achieved significantly greater HDL-raising compared to lovastatin and niacin extended-release tablets monotherapy at all doses (Table 8).

Table 8. HDL-C Mean Percent Change From Baseline

Week	Combination Tablet of Niacin Extended-Release Tablets and Lovastatin			Niacin Extended-Release Tablets			Lovastatin		
	n*	Dose (mg/mg)	HDL	n*	Dose (mg)	HDL	n*	Dose (mg)	HDL
Baseline	57	-	45 mg/dL	61	-	47 mg/dL	61	-	43 mg/dL
12	47	1000/20	+20%	46	1000	+14%	56	20	+3%
16	45	1000/40	+20%	44	1000	+15%	56	40	+5%
20	42	1500/40	+27%	43	1500	+22%	54	40	+6%
28	42	2000/40	+30%	41	2000	+24%	53	40	+6%

* n = number of patients remaining in trial at each time point

In addition, combination therapy achieved significantly greater TG-lowering at doses of 1000 mg/20 mg or greater compared to lovastatin and niacin extended-release tablets monotherapy (Table 9).

Table 9. TG Median Percent Change From Baseline

Week	Combination Tablet of Niacin Extended-Release Tablets and Lovastatin			Niacin Extended-Release Tablets			Lovastatin		
	n*	Dose (mg/mg)	TG	n*	Dose (mg)	TG	n*	Dose (mg)	TG
Baseline	57	-	174 mg/dL	61	-	186 mg/dL	61	-	171 mg/dL
12	47	1000/20	-32%	46	1000	-22%	56	20	-20%
16	45	1000/40	-39%	44	1000	-23%	56	40	-17%
20	42	1500/40	-44%	43	1500	-31%	54	40	-21%
28	42	2000/40	-44%	41	2000	-31%	53	40	-20%

* n = number of patients remaining in trial at each time point

The Lp(a)-lowering effects of combination therapy and niacin extended-release tablets monotherapy were similar, and both were superior to lovastatin (Table 10). The independent effect of lowering Lp(a) with niacin extended-release tablets or combination therapy on the risk of coronary and cardiovascular morbidity and mortality has not been determined.

Table 10. Lp(a) Median Percent Change From Baseline

Week	Combination Tablet of Niacin Extended-Release Tablets and Lovastatin			Niacin Extended-Release Tablets			Lovastatin		
	n*	Dose (mg/mg)	Lp(a)	n*	Dose (mg)	Lp(a)	n*	Dose (mg)	Lp(a)
Baseline	57	-	34 mg/dL	61	-	41 mg/dL	60	-	42 mg/dL
12	47	1000/20	-9%	46	1000	-8%	55	20	+8%
16	45	1000/40	-9%	44	1000	-12%	55	40	+8%
20	42	1500/40	-17%	43	1500	-22%	53	40	+6%
28	42	2000/40	-22%	41	2000	-32%	52	40	0%

* n = number of patients remaining in trial at each time point

INDICATIONS AND USAGE:

Therapy with lipid-altering agents should be only one component of multiple risk factor intervention in individuals at significantly increased risk for atherosclerotic vascular disease due to hypercholesterolemia. Niacin therapy is indicated as an adjunct to diet when the response to a diet restricted in saturated fat and cholesterol and other nonpharmacologic measures alone has been inadequate (see also the NCEP treatment guidelines[8]; Table 11). Prior to initiating therapy with niacin, secondary causes for hypercholesterolemia (e.g., poorly controlled diabetes mellitus, hypothyroidism, nephrotic syndrome, dysproteinemias, obstructive liver disease, other drug therapy, alcoholism) should be excluded, and a lipid profile obtained to measure TC, HDL-C, and TG.

1. Niacin extended-release tablets are indicated as an adjunct to diet for reduction of elevated TC, LDL-C, Apo B and TG levels, and to increase HDL-C in patients with primary hypercholesterolemia (heterozygous familial and nonfamilial) and mixed dyslipidemia (Frederickson Types IIa and IIb; Table 12), when the response to an appropriate diet has been inadequate.

2. Niacin extended-release tablets in combination with lovastatin are indicated for the treatment of primary hypercholesterolemia (heterozygous familial and nonfamilial) and mixed dyslipidemia (Frederickson Types IIa and IIb; Table 12) in:

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

Combination therapy is not indicated as initial therapy. (See DOSAGE and ADMINISTRATION.)

3. In patients with a history of myocardial infarction and hypercholesterolemia, niacin is indicated to reduce the risk of recurrent nonfatal myocardial infarction.

4. In patients with a history of coronary artery disease (CAD) and hypercholesterolemia, niacin, in combination with a bile acid binding resin, is indicated to slow progression or promote regression of atherosclerotic disease.

5. Niacin Extended-Release Tablets in combination with a bile acid binding resin are indicated as an adjunct to diet for reduction of elevated TC and LDL-C levels in adult patients with primary hypercholesterolemia (Type IIa; Table 12), when the response to an appropriate diet, or diet plus monotherapy, has been inadequate.

6. Niacin is also indicated as adjunctive therapy for treatment of adult patients with very high serum triglyceride levels (Types IV and V hyperlipidemia; Table 12) who present a risk of pancreatitis and who do not respond adequately to a determined dietary effort to control them. Such patients typically have serum TG levels over 2000 mg/dL and have elevations of VLDL-C as well as fasting chylomicrons (Type V hyperlipidemia; Table 12). Patients who consistently have total serum or plasma TG below 1000 mg/dL are unlikely to develop pancreatitis. Therapy with niacin may be considered for those patients with TG elevations between 1000 and 2000 mg/dL who have a history of pancreatitis or of recurrent abdominal pain typical of pancreatitis. Some Type IV patients with TG under 1000 mg/dL may, through dietary or alcohol indiscretion, convert to a Type V pattern with massive TG elevations accompanying fasting chylomicronemia, but the influence of niacin therapy on risk of pancreatitis in such situations has not been adequately studied. Drug therapy is not indicated for patients with Type I hyperlipoproteinemia, who have elevations of chylomicrons and plasma TG, but who have normal levels of VLDL-C. Inspection of plasma refrigerated for 14 hours is helpful in distinguishing Types I, IV, and V hyperlipoproteinemia.[9]

Table 11. NCEP Treatment Guidelines: LDL-C Goals and Cutpoints for Therapeutic Lifestyle Changes and Drug Therapy in Different Risk Categories

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

† CHD, coronary heart disease

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

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

After the LDL-C goal has been achieved, if the TG is still ≥200 mg/dL, non-HDL-C (TC minus HDL-C) becomes a secondary target of therapy. Non-HDL-C goals are set 30 mg/dL higher than LDL-C goals for each risk category.

Table 12. Classification of Hyperlipoproteinemias

		Lipid Elevations	
Type	Lipoproteins Elevated	Major	Minor
I (rare)	chylomicrons	TG	↑→TC
IIa	LDL	TC	-
IIb	LDL, VLDL	TC	TG
III (rare)	IDL	TC/TG	-
IV	VLDL	TG	↑→TC
V (rare)	chylomicrons, VLDL	TG	↑→TC

TC = total cholesterol; TG = triglycerides; LDL = low-density lipoprotein;
VLDL = very low-density lipoprotein; IDL = intermediate-density lipoprotein
↑→ = increased or no change

CONTRAINDICATIONS:

Niacin extended-release tablets are contraindicated in patients with a known hypersensitivity to niacin or any component of this medication, significant or unexplained hepatic dysfunction, active peptic ulcer disease, or arterial bleeding.

WARNINGS:

Niacin extended-release tablets preparations should not be substituted for equivalent doses of immediate-release (crystalline) niacin. For patients switching from immediate-release niacin to niacin extended-release tablets, therapy with niacin extended-release tablets should be initiated with low doses (i.e., 500 mg qhs) and the niacin extended-release tablets dose should then be titrated to the desired therapeutic response (see DOSAGE AND ADMINISTRATION).

Liver Dysfunction:

Cases of severe hepatic toxicity, including fulminant hepatic necrosis, have occurred in patients who have substituted sustained-release (modified-release, timed-release) niacin products for immediate-release (crystalline) niacin at equivalent doses.

Niacin extended-release tablets should be used with caution in patients who consume substantial quantities of alcohol and/or have a past history of liver disease. Active liver diseases or unexplained transaminase elevations are contraindications to the use of niacin extended-release tablets.

Niacin preparations, like some other lipid-lowering therapies, have been associated with abnormal liver tests. In three placebo-controlled clinical trials involving titration to final daily niacin extended-release tablets doses ranging from 500 to 3000 mg, 245 patients received niacin extended-release tablets for a mean duration of 17 weeks. No patient with normal serum transaminase levels (AST, ALT) at baseline experienced elevations to more than 3 times the upper limit of normal (ULN) during treatment with niacin extended-release tablets. In these studies, fewer than 1% (2/245) of niacin extended-release tablets patients discontinued due to transaminase elevations greater than 2 times the ULN.

In three safety and efficacy studies with a combination tablet of niacin extended-release tablets and lovastatin involving titration to final daily doses (expressed as mg of niacin extended-release tablets/mg of lovastatin) 500 mg/10 mg to 2500 mg/40 mg, ten of 1028 patients (1.0%) experienced reversible elevations in AST/ALT to more than 3 times the upper limit of normal (ULN). Three of ten elevations occurred at doses outside the recommended dosing limit of 2000 mg/40 mg; no patient receiving 1000 mg/20 mg had 3-fold elevations in AST/ALT.

In the placebo-controlled clinical trials and the long-term extension study, elevations in transaminases did not appear to be related to treatment duration; elevations in AST levels did appear to be dose related. Transaminase elevations were reversible upon discontinuation of niacin extended-release tablets.

Liver tests should be performed on all patients during therapy with niacin extended-release tablets. Serum transaminase levels, including AST and ALT (SGOT and SGPT), should be monitored before treatment begins, every 6 weeks to 12 weeks for the first year, and periodically thereafter (e.g., at approximately 6-month intervals). Special attention should be paid to patients who develop elevated serum transaminase levels, and in these patients, measurements should be repeated promptly and then performed more frequently. If the transaminase levels show evidence of progression, particularly if they rise to 3 times ULN and are persistent, or if they are associated with symptoms of nausea, fever, and/or malaise, the drug should be discontinued.

Skeletal Muscle:

Rare cases of rhabdomyolysis have been associated with concomitant administration of lipid-altering doses (≥1 g/day) of niacin and HMG-CoA reductase inhibitors. In clinical studies with a combination tablet of niacin extended-release tablets and lovastatin, no cases of rhabdomyolysis and one suspected case of myopathy have been reported in 1079 patients who were treated with doses up to 2000 mg of niacin extended-release tablets and 40 mg of lovastatin daily for periods up to 2 years. Physicians contemplating combined therapy with HMG-CoA reductase inhibitors and niacin extended-release tablets should carefully weigh the potential benefits and risks and should carefully monitor patients for any signs and symptoms of muscle pain, tenderness, or weakness, particularly during the initial months of therapy and during any periods of upward dosage titration of either drug. Periodic serum creatine phosphokinase (CPK) and potassium determinations should be considered in such situations, but there is no assurance that such monitoring will prevent the occurrence of severe myopathy.

PRECAUTIONS:

General:

Before instituting therapy with niacin extended-release tablets, an attempt should be made to control hyperlipidemia with appropriate diet, exercise, and weight reduction in obese patients, and to treat other underlying medical problems (see INDICATIONS AND USAGE).

Patients with a past history of jaundice, hepatobiliary disease, or peptic ulcer should be observed closely during niacin extended-release tablets therapy. Frequent monitoring of liver function tests and blood glucose should be performed to ascertain that the drug is producing no adverse effects on these organ systems. Diabetic patients may experience a dose-related rise in glucose intolerance, the clinical significance of which is unclear. Diabetic or potentially diabetic patients should be observed closely. Adjustment of diet and/or hypoglycemic therapy may be necessary.

Caution should also be used when niacin extended-release tablets are used in patients with unstable angina or in the acute phase of MI, particularly when such patients are also receiving vasoactive drugs such as nitrates, calcium channel blockers, or adrenergic blocking agents.

Elevated uric acid levels have occurred with niacin therapy, therefore use with caution in patients predisposed to gout.

Niacin extended-release tablets have been associated with small but statistically significant dose-related reductions in platelet count (mean of -11% with 2000 mg). In addition, niacin extended-release tablets have been associated with small but statistically significant increases in prothrombin time (mean of approximately +4%); accordingly, patients undergoing surgery should be carefully evaluated. Caution should be observed when niacin extended-release tablets are administered concomitantly with anticoagulants; prothrombin time and platelet counts should be monitored closely in such patients.

In placebo-controlled trials, niacin extended-release tablets have been associated with small but statistically significant, dose-related reductions in phosphorus levels (mean of -13% with 2000 mg). Although these reductions were transient, phosphorus levels should be monitored periodically in patients at risk for hypophosphatemia.

Niacin is rapidly metabolized by the liver, and excreted through the kidneys. Niacin extended-release tablets are contraindicated in patients with significant or unexplained hepatic dysfunction (see CONTRAINDICATIONS and WARNINGS) and should be used with caution in patients with renal dysfunction.

Information for Patients:

Patients should be advised:

• to take niacin extended-release tablets at bedtime, after a low-fat snack. Administration on an empty stomach is not recommended;

• to carefully follow the prescribed dosing regimen, including the recommended titration schedule, in order to minimize side effects (see DOSAGE AND ADMINISTRATION);

• that flushing is a common side effect of niacin therapy that usually subsides after several weeks of consistent niacin use. Flushing may vary in severity, may last for several hours after dosing, and will, by taking niacin extended-release tablets at bedtime, most likely occur during sleep; however, if awakened by flushing at night, to get up slowly, especially if feeling dizzy, feeling faint, or taking blood pressure medications;

(Over)

• that taking aspirin (approximately 30 minutes before taking niacin extended-release tablets) or a non-steroidal anti-inflammatory drug (e.g., ibuprofen) may minimize flushing;
• to avoid ingestion of alcohol or hot drinks around the time of niacin extended-release tablets administration, to minimize flushing;
• that if niacin extended-release tablets therapy is discontinued for an extended length of time, their physician should be contacted prior to re-starting therapy; re-titration is recommended (see DOSAGE AND ADMINISTRATION; Table 14);
• to notify their physician if they are taking vitamins or other nutritional supplements containing niacin or related compounds such as nicotinamide (see Drug Interactions);
• to notify their physician if symptoms of dizziness occur;
• if diabetic, to notify their physician of changes in blood glucose;
• that niacin extended-release tablets should not be broken, crushed or chewed, but should be swallowed whole.

Drug Interactions:

HMG-CoA Reductase Inhibitors: See WARNINGS, Skeletal Muscle.

Antihypertensive Therapy: Niacin may potentiate the effects of ganglionic blocking agents and vasoactive drugs resulting in postural hypotension.

Aspirin: Concomitant aspirin may decrease the metabolic clearance of nicotinic acid. The clinical relevance of this finding is unclear.

Bile Acid Sequestrants: An *in vitro* study was carried out investigating the niacin-binding capacity of colestipol and cholestyramine. About 98% of available niacin was bound to colestipol, with 10 to 30% binding to cholestyramine. These results suggest that 4 to 6 hours, or as great an interval as possible, should elapse between the ingestion of bile acid-binding resins and the administration of niacin extended-release tablets.

Other: Concomitant alcohol or hot drinks may increase the side effects of flushing and pruritus and should be avoided around the time of niacin extended-release tablets ingestion. Vitamins or other nutritional supplements containing large doses of niacin or related compounds such as nicotinamide may potentiate the adverse effects of niacin extended-release tablets.

Drug/Laboratory Test Interactions:

Niacin may produce false elevations in some fluorometric determinations of plasma or urinary catecholamines. Niacin may also give false-positive reactions with cupric sulfate solution (Benedict's reagent) in urine glucose tests.

Carcinogenesis, Mutagenesis, Impairment of Fertility:

Niacin administered to mice for a lifetime as a 1% solution in drinking water was not carcinogenic. The mice in this study received approximately 6 to 8 times a human dose of 3000 mg/day as determined on a mg/m^2 basis. Niacin was negative for mutagenicity in the Ames test. No studies on impairment of fertility have been performed. No studies have been conducted with niacin extended-release tablets regarding carcinogenesis, mutagenesis, or impairment of fertility.

Pregnancy:

Pregnancy Category C: Animal reproduction studies have not been conducted with niacin or with niacin extended-release tablets. It is also not known whether niacin at doses typically used for lipid disorders can cause fetal harm when administered to pregnant women or whether it can affect reproductive capacity. If a woman receiving niacin for primary hypercholesterolemia (Types IIa or IIb) becomes pregnant, the drug should be discontinued. If a woman being treated with niacin for hypertriglyceridemia (Types IV or V) conceives, the benefits and risks of continued therapy should be assessed on an individual basis.

Nursing Mothers:

Niacin has been reported to be excreted in human milk. Because of the potential for serious adverse reactions in nursing infants from lipid-altering doses of nicotinic acid, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother. No studies have been conducted with niacin extended-release tablets in nursing mothers.

Pediatric Use:

Safety and effectiveness of niacin therapy in pediatric patients (≤16 years) have not been established. No studies in patients under 21 years of age have been conducted with niacin extended-release tablets.

ADVERSE REACTIONS:

Niacin extended-release tablets are generally well tolerated; adverse reactions have been mild and transient. In the placebo-controlled clinical trials, flushing episodes (i.e., warmth, redness, itching and/or tingling) were the most common treatment-emergent adverse events (reported by as many as 88% of patients) for niacin extended-release tablets. Spontaneous reports suggest that flushing may also be accompanied by symptoms of dizziness, tachycardia, palpitations, shortness of breath, sweating, chills, and/or edema, which in rare cases may lead to syncope. In pivotal studies, fewer that 6% (14/245) of niacin extended-release tablets patients discontinued due to flushing. In comparisons of immediate-release (IR) niacin and niacin extended-release tablets, although the proportion of patients who flushed was similar, fewer flushing episodes were reported by patients who received niacin extended-release tablets. Following 4 weeks of maintenance therapy at daily doses of 1500 mg, the incidence of flushing over the 4-week period averaged 8.56 events per patient for IR niacin versus 1.88 following niacin extended-release tablets.

Other adverse events occurring in 5% or greater of patients treated with niacin extended-release tablets, at least remotely related to niacin extended-release tablets, are shown in Table 13 below.

Table 13. Treatment-Emergent Adverse Events by Dose Level in ≥5% of Patients; Events Considered At Least Remotely Related to Study Medication

	Placebo-Controlled Studies Niacin Extended-Release Tablets Treatment†						
			Recommended Daily Maintenance Doses			Greater Than Recommended Daily Doses	
	Placebo (n=157) %	500 mg‡ (n=87) %	1000 mg (n=110) %	1500 mg (n=136) %	2000 mg (n=95) %	2500 mg‡ (n=49) %	3000 mg‡ (n=46) %
Headache	15	5*	9	11	8	4*	4
Pain	3	1	2	5	3	0	2
Pain, Abdominal	3	3	2	3	5	0	0
Diarrhea	8	6	7	6	8	10	11
Dyspepsia	8	2	4	5	5	6	0
Nausea	4	2	5	3	8	10	4
Vomiting	2	0	2	3	8*	8	2
Rhinitis	7	2	5	4	3	0	0
Pruritus	1	6	<1	3	1	0	0
Rash	<1	5	5	4	0	0	0

Note: Percentages are calculated from the total number of patients in each column. AEs are reported at the lowest dose where they occurred.

† Pooled results from placebo-controlled studies; for Niacin Extended-Release Tablets, n = 245 and mean treatment duration = 17 weeks. Number of Niacin Extended-Release Tablets patients (n) are not additive across doses.

‡ The 500 mg, 2500 mg and 3000 mg/day doses are outside the recommended daily maintenance dosing range; see DOSAGE AND ADMINISTRATION.

* Significantly different from placebo at $p \leq 0.05$; Chi-square test (cell size >5), Fisher's Exact test (cell sizes ≤5).

In general, the incidence of adverse events was higher in women compared to men.

The following adverse events have also been reported with niacin products, either during clinical trials or in routine patient management.

Body as a Whole: edema, asthenia, chills

Cardiovascular: atrial fibrillation, and other cardiac arrhythmias; tachycardia, palpitations; orthostasis; syncope; hypotension

Eye: toxic amblyopia, cystoid macular edema

Gastrointestinal: activation of peptic ulcers and peptic ulceration; jaundice

Metabolic: decreased glucose tolerance; gout

Musculoskeletal: myalgia

Nervous: dizziness, insomnia

Skin: hyper-pigmentation; acanthosis nigricans; maculopapular rash; urticaria; dry skin; sweating

Other: migraine

Clinical Laboratory Abnormalities:

Chemistry: Elevations in serum transaminases (see WARNINGS, Liver Dysfunction), LDH, fasting glucose, uric acid, total bilirubin, and amylase; reductions in phosphorus

Hematology: Slight reductions in platelet counts and prolongation in prothrombin time (see WARNINGS)

DRUG ABUSE AND DEPENDENCE:

Niacin is a non-narcotic drug. It has no known addiction potential in humans.

OVERDOSAGE:

Supportive measures should be undertaken in the event of an overdose.

DOSAGE AND ADMINISTRATION:

Niacin Extended-Release Tablets should be taken at bedtime, after a low-fat snack, and doses should be individualized according to patient response. Therapy with Niacin Extended-Release Tablets must be initiated at 500 mg qhs in order to reduce the incidence and severity of side effects which may occur during early therapy. The recommended dose escalation is shown in Table 14 below.

Table 14. Recommended Dosing

	Week(s)	Daily dose	Niacin Extended-Release Tablets Dosage
INITIAL TITRATION	1 to 4	500 mg	1 Niacin Extended-Release Tablet 500 mg at bedtime
	5 to 8	1000 mg	2 Niacin Extended-Release Tablets 500 mg at bedtime
	*	1500 mg	2 Niacin Extended-Release Tablets 750 mg or 3 Niacin Extended-Release Tablets 500 mg at bedtime
	*	2000 mg	2 Niacin Extended-Release Tablets 1000 mg or 4 Niacin Extended-Release Tablets 500 mg at bedtime

* After Week 8, titrate to patient response and tolerance. If response to 1000 mg daily is inadequate, increase dose to 1500 mg daily; may subsequently increase dose to 2000 mg daily. Daily dose should not be increased more than 500 mg in a 4-week period, and doses above 2000 mg daily are not recommended. Women may respond at lower doses than men.

Maintenance Dose:

The daily dosage of Niacin Extended-Release Tablets should not be increased by more than 500 mg in any 4-week period. The recommended maintenance dose is 1000 mg (two 500 mg tablets) to 2000 mg (two 1000 mg tablets or four 500 mg tablets) once daily at bedtime. Doses greater than 2000 mg daily are not recommended. Women may respond at lower Niacin Extended-Release Tablets doses than men (see CLINICAL PHARMACOLOGY, Gender Effect).

If lipid response to Niacin Extended-Release Tablets alone is insufficient (see NCEP treatment guidelines; Table 11), or if higher doses of Niacin Extended-Release Tablets are not well tolerated, some patients may benefit from combination therapy with a bile acid binding resin or an HMG-CoA reductase inhibitor. (see WARNINGS, PRECAUTIONS, Drug Interactions, Concomitant Therapy below, and CLINICAL PHARMACOLOGY, Niacin Extended-Release Tablets Clinical Studies)

Flushing of the skin (see ADVERSE REACTIONS) may be reduced in frequency or severity by pretreatment with aspirin (taken 30 minutes prior to Niacin Extended-Release Tablets dose) or non-steroidal anti-inflammatory drugs. Tolerance to this flushing develops rapidly over the course of several weeks. Flushing, pruritus, and gastrointestinal distress are also greatly reduced by slowly increasing the dose of niacin and avoiding administration on an empty stomach.

Equivalent doses of Niacin Extended-Release Tablets should **not** be substituted for sustained-release (modified-release, timed-release) niacin preparations or immediate-release (crystalline) niacin (see WARNINGS). Patients previously receiving other niacin products should be started with the recommended Niacin Extended-Release Tablets titration schedule (see Table 14), and the dose should subsequently be individualized based on patient response. Single-dose bioavailability studies have demonstrated that Niacin Extended-Release Tablets strengths are not interchangeable.

If Niacin Extended-Release Tablets therapy is discontinued for an extended period, reinstitution of therapy should include a titration phase (see Table 14).

Niacin Extended-Release Tablets should be taken whole and should not be broken, crushed or chewed before swallowing.

Concomitant Therapy:

Concomitant Therapy with Lovastatin: Patients already receiving a stable dose of lovastatin who require further TG-lowering or HDL-raising (e.g., to achieve NCEP non-HDL-C goals), may receive concomitant dosage titration with Niacin Extended-Release Tablets per Niacin Extended-Release Tablets recommended initial titration schedule (see Table 14, DOSAGE AND ADMINISTRATION section). For patients already receiving a stable dose of Niacin Extended-Release Tablets who require further LDL-lowering (e.g., to achieve NCEP LDL-C goals; Table 11), the usual recommended starting dose of lovastatin is 20 mg once a day. Dose adjustments should be made at intervals of 4 weeks or more. Combination therapy with Niacin Extended-Release Tablets and lovastatin should not exceed doses of 2000 mg and 40 mg daily, respectively.

Dosage in Patients with Renal or Hepatic Insufficiency:

Use of Niacin Extended-Release Tablets in patients with renal or hepatic insufficiency has not been studied. Niacin Extended-Release Tablets are contraindicated in patients with significant or unexplained hepatic dysfunction. Niacin Extended-Release Tablets should be used with caution in patients with renal insufficiency (see WARNINGS, PRECAUTIONS).

HOW SUPPLIED:

Niacin Extended-Release Tablets are available as:

1000 mg: White to off-white, capsule-shaped, unscored, biconvex tablet. Debossed with **b 214** on one side and **1000** on the other side. Available in bottles of:
100 NDC 0555-0214-02
250 NDC 0555-0214-03

Dispense in a tight container with a child-resistant closure.

Store at 20° to 25°C (68° to 77°F) [See USP Controlled Room Temperature].

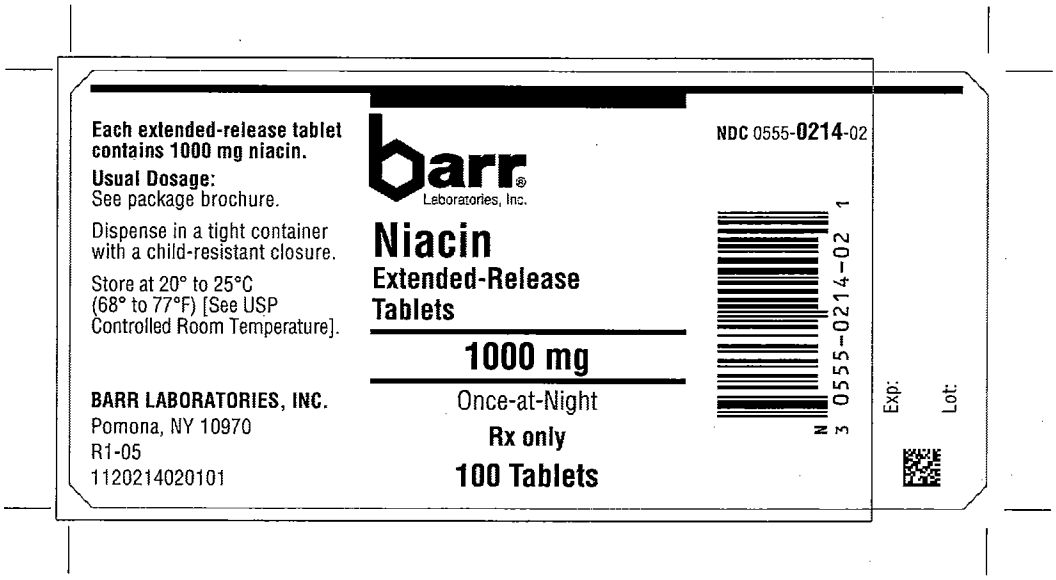
REFERENCES:

1. Bostom AG et al. *JAMA* 1996; 276:544-548.
2. The Coronary Drug Project Research Group. *JAMA* 1975; 231:360-381.
3. Canner PL et al. *J Am Coll Cardiol* 1986; 8(6):1245-1255.
4. Blankenhorn DH et al. *JAMA* 1987; 257(23):3233-3240.
5. Cashin-Hemphill L et al. *JAMA* 1990; 264(23):3013-3017.
6. Brown G et al. *N Engl J Med* 1990; 323:1289-1298.
7. Pasternak RC et al. *Annals Int Med* 1996; 125:529-540.
8. Executive Summary of the Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III), *JAMA* 2001;285:2486-2497.
9. Nikkila EA, In: *The Metabolic Basis of Inherited Disease*, 5th ed. Chap. 30: 622-642.1983.

MANUFACTURED BY
BARR LABORATORIES, INC.
POMONA, NY 10970
Revised JANUARY 2005
BR-214

proof approval form | *proof date: 01/22/05*

Phone



■ Black ■ Skip Varnish

■ PMS 293 ■ Die Strike

Customer: Barr

PO#:

Job #: 147870-3

Size: 5" x 2.375"

Comments: 5/8" Skip Varnish Area

	PROOFED BY:	DATE
INITIAL SET BY:		
CORRECTED BY:		
CLIENTS APPROVAL BY:		
PRIVATE CUSTOMER APPROVAL BY:		

proof approval form | *proof date: 01/22/05*

Phone /

Each extended-release tablet contains 1000 mg niacin.

Usual Dosage:
See package brochure.

Dispense in a tight container with a child-resistant closure.

Store at 20° to 25°C (68° to 77°F) [See USP Controlled Room Temperature].

BARR LABORATORIES, INC.
Pomona, NY 10970

R1-05
1120214030101

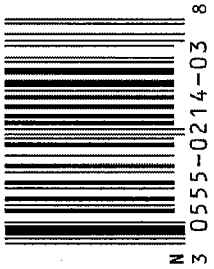
barr®
Laboratories, Inc.

Niacin
Extended-Release Tablets

1000 mg

Once-at-Night
Rx only
250 Tablets

NDC 0555-**0214**-03



Exp:

Lot:

■ Black ■ Skip Varnish
■ PMS 293 ■ Die Strike

Customer: Barr
PO#:
Job #: 147874-3
Size: 7" x 3.625"
Comments: 5/8" Skip Varnish Area

	PROOFED BY:	DATE
INITIAL SET BY:		
CORRECTED BY:		
CLIENTS APPROVAL BY:		
PRIVATE CUSTOMER APPROVAL BY:		

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 76-250

LABELING REVIEWS

REVIEW OF PROFESSIONAL LABELING#1
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH

ANDA Number: **76-250** Date of Submission: October 2, 2001
Applicant's Name: Barr
Established Name: **Niacin Extended-release Tablets 1000 mg**

Labeling Deficiencies:

1. CONTAINER - Revise the Each tablet contains statement as folllows:

   Each Extended-release tablet contains 1000 mg niacin.

2. .PROFESSIONAL INSERT - Satisfactory in draft.

Please revise your labels and labeling, as instructed above, and submit 12 final printed labels and labeling or draft labeling if you prefer.

Prior to approval, it may be necessary to further revise your labeling subsequent to approved changes for the reference listed drug. We suggest that you routinely monitor the following website for any approved changes - http://www.fda.gov/cder/ogd/rld/labeling_review_branch.html

To facilitate review of your next submission, and in accordance with 21 CFR 314.94(a)(8)(iv), please provide a side-by-side comparison of your labeling with your last submission with all differences annotated and explained.

Wm. Peter Rickman
Acting Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

APPROVAL SUMMARY (List the package size, strength(s), and date of submission for approval):Do you have 12 Final Printed Labels and Labeling? Yes No If no, list why:
Container Labels:
Carton Labeling:
Unit Dose Blister Label:
Unit Dose Carton Label:
Professional Package Insert Labeling:
Patient Package Insert Labeling:-
Auxiliary Labeling:
Revisions needed post-approval:
BASIS OF APPROVAL:

Patent Data For NDA 20-381 004

Patent No	Patent Expiration	Use Code	Description	How Filed	Labeling Impact
6080428	May 27, 2017	U-331	METHOD OF TREATING HYPERLIPIDEMIA WITH NICOTINIC ACID BY DOSING ONCE PER DAY IN THE EVENING OR AT NIGHT	P-IV	SAME AS
6129930	Sep.20,2013	U-354	METHOD OF TREATING HYPERLIPIDEMIA WITH NICOTINIC ACID WITHOUT CAUSING TREATMENT-LIMITING ELEVATIONS IN URIC ACID OR GLUCOSE LEVELS OR CAUSING LIVER DAMAGE, BY DOSING ONCE PER DAY IN THE EVENING OR AT	P-IV	SAME AS

Exclusivity Data For NDA

Code/sup	Expiration	Description	Labeling impact
NONE		NONE	NONE

Was this approval based upon a petition? No
What is the RLD on the 356(h) form: NIASPAN
NDA Number: 20381
NDA Drug Name: Niacin ER tablets
NDA Firm: Kos Pharmaceuticals
Date of Approval of NDA Insert and supplement #: S-007 & 006app. 9/13/99 and 10/28/99 respectively
Has this been verified by the MIS system for the NDA? Yes
Was this approval based upon an OGD labeling guidance? No
Basis of Approval for the Container Labels: sample in jacket
Basis of Approval for the Carton Labeling: sample in jacket
Other Comments: The name of the generic product should reflect the USP monograph for tablets. A statement with asterisk should accompany the strength to desiginate it as Extended Release form.

REVIEW OF PROFESSIONAL LABELING CHECK LIST

Established Name	Yes	No	N.A.
Different name than on acceptance to file letter?		X	
Is this product a USP item? If so, USP supplement in which verification was assured. USP 23		X	
Is this name different than that used in the Orange Book?		X	
If not USP, has the product name been proposed in the PF?			X
Error Prevention Analysis			
Has the firm proposed a proprietary name? If yes, complete this subsection.		X	
Do you find the name objectionable? List reasons in FTR, if so. Consider: Misleading? Sounds or looks like another name? USAN stem present? Prefix or Suffix present?			X
Has the name been forwarded to the Labeling and Nomenclature Committee? If so, what were the recommendations? If the name was unacceptable, has the firm been notified?			X
Packaging			
Is this a new packaging configuration, never been approved by an ANDA or NDA? If yes, describe in FTR.	x		
Is this package size mismatched with the recommended dosage? If yes, the Poison Prevention Act may require a CRC.		X	
Does the package proposed have any safety and/or regulatory concerns?		X	
If IV product packaged in syringe, could there be adverse patient outcome if given by direct IV injection?		X	
Conflict between the DOSAGE AND ADMINISTRATION and INDICATIONS sections and the packaging configuration?		X	
Is the strength and/or concentration of the product unsupported by the insert labeling?		X	
Is the color of the container (i.e. the color of the cap of a mydriatic ophthalmic) or cap incorrect?		X	
Individual cartons required? Issues for FTR: Innovator individually cartoned? Light sensitive product which might require cartoning? Must the package insert accompany the product?		X	
Are there any other safety concerns?		X	
Labeling			
Is the name of the drug unclear in print or lacking in prominence? (Name should be the most prominent information on the label).	X		
Has applicant failed to clearly differentiate multiple product strengths?			X
Is the corporate logo larger than 1/3 container label? (No regulation - see ASHP guidelines)		X	
Labeling(continued)	Yes	No	N.A.
Does RLD make special differentiation for this label? (i.e., Pediatric strength vs Adult; Oral Solution vs Concentrate, Warning Statements that might be in red for the NDA)	X	X	
Is the Manufactured by/Distributor statement incorrect or falsely inconsistent between labels and labeling? Is "Jointly Manufactured by...", statement needed?		X	
Failure to describe solid oral dosage form identifying markings in HOW SUPPLIED?		X	
Has the firm failed to adequately support compatibility or stability claims which appear in the insert labeling? Note: Chemist should confirm the data has been adequately supported.		X	
Scoring: Describe scoring configuration of RLD and applicant (page #) in the FTR			
Is the scoring configuration different than the RLD?		X	
Has the firm failed to describe the scoring in the HOW SUPPLIED section?		X	
Inactive Ingredients: (FTR: List page # in application where inactives are listed)			
Does the product contain alcohol? If so, has the accuracy of the statement been confirmed?		X	
Do any of the inactives differ in concentration for this route of administration?		X	
Any adverse effects anticipated from inactives (i.e., benzyl alcohol in neonates)?		X	
Is there a discrepancy in inactives between DESCRIPTION and the composition statement?		X	
Has the term "other ingredients" been used to protect a trade secret? If so, is claim supported?		X	
Failure to list the coloring agents if the composition statement lists e.g., Opacode, Opaspray?			X
Failure to list gelatin, coloring agents, antimicrobials for capsules in DESCRIPTION?			X
Failure to list dyes in imprinting inks? (Coloring agents e.g., iron oxides need not be listed)			X
USP Issues: (FTR: List USP/NDA/ANDA dispensing/storage recommendations)			
Do container recommendations fail to meet or exceed USP/NDA recommendations? If so, are the recommendations supported and is the difference acceptable?		X	

Because of proposed packaging configuration or for any other reason, does this applicant meet fail to meet all of the unprotected conditions of use of referenced by the RLD?		X	
Does USP have labeling recommendations? If any, does ANDA meet them?		X	
Is the product light sensitive? If so, is NDA and/or ANDA in a light resistant container?		X	
Failure of DESCRIPTION to meet USP Description and Solubility information? If so, USP information should be used. However, only include solvents appearing in innovator labeling.		X	
Bioequivalence Issues: (Compare bioequivalency values: insert to study. List Cmax, Tmax, T 1/2 and date study acceptable)			
Insert labeling references a food effect or a no-effect? If so, was a food study done?	x		
Has CLINICAL PHARMACOLOGY been modified? If so, briefly detail where/why.		X	
Patent/Exclusivity Issues?: FTR: Check the Orange Book edition or cumulative supplement for verification of the latest Patent or Exclusivity. List expiration date for all patents, exclusivities, etc. or if none, please state.	X		

NOTES/QUESTIONS TO THE CHEMIST:

FOR THE RECORD:

1. Review based on the labeling of Niaspan; Kos pharm. 20381/S-006 & 007, S-007 & 006app. 9/13/99 and 10/28/99 respectively.
2. Patent/ Exclusivities - See above chart
2. Storage Conditions:
   NDA –RT
   ANDA – same
   USP -
4. Dispensing Recommendations:
   NDA – a tight container with CRC
   ANDA - same
   USP -
5. Scoring:
   NDA - unscored
   ANDA - unscored
   USP -
6. Product Line:
   The innovator markets their product in 500 mg, 750 mg, 1000 mg ER, bottles of 100s
   The applicant proposes to market their product 100 mg ER in bottles of 100s with CRC and 250s
7. The tablet/capsule imprint(ings)/embossing(s)/ debossing(s) has/have been accurately described in the HOW SUPPLIED section as required by 21 CFR
8. Inactive Ingredients:
   The listing of inactive ingredients in the DESCRIPTION section of the package insert appears to be consistent with the listing of inactive ingredients found in the statement of components and composition appearing on page 07-3 vol 1.1 red.
9. Manufactured by Barr.
10. Bio division found generic product to be equivalent to RLD.

Date of Review: January 7, 2002 **Date of Submission: October 2, 2001**

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cc: ANDA: 76-250
DUP/DIVISION FILE
HFD-613/APayne/JGrace (no cc)
V:firmsam/Barr/lets&rev/76250na1.L
Review

01-08/02

1/9/2002

Tentative APPROVAL SUMMARY
REVIEW OF PROFESSIONAL LABELING
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH

ANDA Number	~~76-250~~
Date of Submission	March 25, 2002
Applicant	Barr
Drug Name	Niacin Extended-release Tablet
Strength(s)	1000 mg

Draft Approval Summary (will require FPL before approval)

Container Labels

1000 mg	100s & 250s	Submitted March 25, 2002, vol.2.1

Package Insert Labeling Submitted October 2, 2001, vol.1.1

BASIS OF APPROVAL: Patent Data For NDA 20-381

Patent No	Patent Expiration	Use Code	Description	How Filed	Labeling Impact
6129930	Sep.20,2013	U-354	METHOD OF TREATING HYPERLIPIDEMIA WITH NICOTINIC ACID WITHOUT CAUSING TREATMENT-LIMITING ELEVATIONS IN URIC ACID OR GLUCOSE LEVELS OR CAUSING LIVER DAMAGE, BY DOSING ONCE PER DAY IN THE EVENING OR AT	P-IV	SAME AS
6080428	May 27, 2017	U-331	METHOD OF TREATING HYPERLIPIDEMIA WITH NICOTINIC ACID BY DOSING ONCE PER DAY IN THE EVENING OR AT NIGHT	P-IV	SAME AS

Exclusivity Data For NDA

Code/sup	Expiration	Description	Labeling impact
none			none

Reference Listed Drug

RLD on the 356(h) form	NIASPAN ®
NDA Number	20-381
RLD established name	Niacin ER tablets
Firm	Kos Pharmaceuticals
Currently approved PI	#: S-007 & 006
AP Date	9/13/99 and 10/28/99 respectively

Δ to SE-13 before full approval.

Note: new labeling approved on 1/31/03 SE-013. Firm will have to revise labeling and certify to patent 4-450 - expire Oct 31, 2017. [signature] 4/29/03

REVIEW OF PROFESSIONAL LABELING CHECK LIST

Established Name	Yes	No	N.A.
Different name than on acceptance to file letter?		X	
Is this product a USP item? If so, USP supplement in which verification was assured. USP 23		X	
Is this name different than that used in the Orange Book?		X	
If not USP, has the product name been proposed in the PF?			X
Error Prevention Analysis			
Has the firm proposed a proprietary name? If yes, complete this subsection.		X	
Do you find the name objectionable? List reasons in FTR, if so. Consider: Misleading? Sounds or looks like another name? USAN stem present? Prefix or Suffix present?			X
Has the name been forwarded to the Labeling and Nomenclature Committee? If so, what were the recommendations? If the name was unacceptable, has the firm been notified?			X
Packaging			
Is this a new packaging configuration, never been approved by an ANDA or NDA? If yes, describe in FTR.	x		
Is this package size mismatched with the recommended dosage? If yes, the Poison Prevention Act may require a CRC.		X	
Does the package proposed have any safety and/or regulatory concerns?		X	
If IV product packaged in syringe, could there be adverse patient outcome if given by direct IV injection?		X	
Conflict between the DOSAGE AND ADMINISTRATION and INDICATIONS sections and the packaging configuration?		X	
Is the strength and/or concentration of the product unsupported by the insert labeling?		X	
Is the color of the container (i.e. the color of the cap of a mydriatic ophthalmic) or cap incorrect?		X	
Individual cartons required? Issues for FTR: Innovator individually cartoned? Light sensitive product which might require cartoning? Must the package insert accompany the product?		X	
Are there any other safety concerns?		X	
Labeling			
Is the name of the drug unclear in print or lacking in prominence? (Name should be the most prominent information on the label).	X		
Has applicant failed to clearly differentiate multiple product strengths?			X
Is the corporate logo larger than 1/3 container label? (No regulation - see ASHP guidelines)		X	
Labeling(continued)	Yes	No	N.A.
Does RLD make special differentiation for this label? (i.e., Pediatric strength vs Adult; Oral Solution vs Concentrate, Warning Statements that might be in red for the NDA)	X	X	
Is the Manufactured by/Distributor statement incorrect or falsely inconsistent between labels and labeling? Is "Jointly Manufactured by...", statement needed?		X	
Failure to describe solid oral dosage form identifying markings in HOW SUPPLIED?		X	
Has the firm failed to adequately support compatibility or stability claims which appear in the insert labeling? Note: Chemist should confirm the data has been adequately supported.		X	
Scoring: Describe scoring configuration of RLD and applicant (page #) in the FTR			
Is the scoring configuration different than the RLD?		X	
Has the firm failed to describe the scoring in the HOW SUPPLIED section?		X	
Inactive Ingredients: (FTR: List page # in application where inactives are listed)			
Does the product contain alcohol? If so, has the accuracy of the statement been confirmed?		X	
Do any of the inactives differ in concentration for this route of administration?		X	
Any adverse effects anticipated from inactives (i.e., benzyl alcohol in neonates)?		X	
Is there a discrepancy in inactives between DESCRIPTION and the composition statement?		X	
Has the term "other ingredients" been used to protect a trade secret? If so, is claim supported?		X	
Failure to list the coloring agents if the composition statement lists e.g., Opacode, Opaspray?			X
Failure to list gelatin, coloring agents, antimicrobials for capsules in DESCRIPTION?			X
Failure to list dyes in imprinting inks? (Coloring agents e.g., iron oxides need not be listed)			X
USP Issues: (FTR: List USP/NDA/ANDA dispensing/storage recommendations)			
Do container recommendations fail to meet or exceed USP/NDA recommendations? If so, are the recommendations supported and is the difference acceptable?		X	
Because of proposed packaging configuration or for any other reason, does this applicant meet fail to meet all of the unprotected conditions of use of referenced by the RLD?		X	
Does USP have labeling recommendations? If any, does ANDA meet them?		X	

Is the product light sensitive? If so, is NDA and/or ANDA in a light resistant container?		X	
Failure of DESCRIPTION to meet USP Description and Solubility information? If so, USP information should be used. However, only include solvents appearing in innovator labeling.		X	
Bioequivalence Issues: (Compare bioequivalency values: insert to study. List Cmax, Tmax, T 1/2 and date study acceptable)			
Insert labeling references a food effect or a no-effect? If so, was a food study done?	x		
Has CLINICAL PHARMACOLOGY been modified? If so, briefly detail where/why.		X	
Patent/Exclusivity Issues?: FTR: Check the Orange Book edition or cumulative supplement for verification of the latest Patent or Exclusivity. List expiration date for all patents, exclusivities, etc. or if none, please state.	X		

NOTES/QUESTIONS TO THE CHEMIST:

FOR THE RECORD:

1. Review based on the labeling of Niaspan; Kos pharm. 20381/S-006 & 007, S-007 & 006app. 9/13/99 and 10/28/99 respectively.
1. Patent/ Exclusivities - See above chart
2. Storage Conditions:
   NDA –RT
   ANDA – same
   USP -
4. Dispensing Recommendations:
   NDA – a tight container with CRC
   ANDA - same
   USP -
5. Scoring:
   NDA - unscored
   ANDA - unscored
   USP -
6. Product Line:
   The innovator markets their product in 500 mg, 750 mg, 1000 mg ER, bottles of 100s
   The applicant proposes to market their product 100 mg ER in bottles of 100s with CRC and 250s
7. The tablet/capsule imprint(ings)/embossing(s)/ debossing(s) has/have been accurately described in the HOW SUPPLIED section as required by 21 CFR
8. Inactive Ingredients:
   The listing of inactive ingredients in the DESCRIPTION section of the package insert appears to be consistent with the listing of inactive ingredients found in the statement of components and composition appearing on page 07-3 vol 1.1 red.
9. Manufactured by Barr.
10. Bio division found generic product to be equivalent to RLD.

Date of Review: April 8, 2002 **Date of Submission: March 25, 2002**

cc: ANDA: 76-250
DUP/DIVISION FILE
HFD-613/APayne/JGrace (no cc)
V:firmsam/Barr/lets&rev/76250tap.L
Review`

4/29/02
4/29/2002

APPROVAL SUMMARY
REVIEW OF PROFESSIONAL LABELING
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH

ANDA Number	76-250
Date of Submission	January 28, 2005
Applicant	Barr
Drug Name	Niacin Extended-release Tablets
Strength(s)	1000 mg

Container Labels	**Submitted e-FPL**
1000 mg - 100s and 250s	\\Cdsesubogd1\n76250\N_000\2005-01-28\labeling\container.pdf
***Package Insert Labeling**	
#1002140101 Rev. 1/05	\\Cdsesubogd1\n76250\N_000\2005-01-28\labeling\brochure.pdf

BASIS OF APPROVAL: Patent Data For NDA 20-381

Patent No	Patent Expiration	Use Code	Description	How Filed	Labeling Impact
6080428	May 27, 2017	U-331	METHOD OF TREATING HYPERLIPIDEMIA WITH NICOTINIC ACID BY DOSING ONCE PER DAY IN THE EVENING OR AT NIGHT	P-IV	SAME AS
6406715	Oct. 17, 2017	U-450	IINTERMEDIATE REL NICOTINIC ACID FORMULATIONS HAVING UNIQUE URINARY METAB PROFILES RESULTING FROM ABSORPTION PROFILES OF NICOTINIC ACID FROM THE INTERMEDIATE NICOTINIC ACID FORMULATIONS, SUITABLE FOR TX HYPERLIPIDEMIA FOLLOWING QD DOSING	PIV	Same As
6129930	Sep.20,2013	U-354	METHOD OF TREATING HYPERLIPIDEMIA WITH NICOTINIC ACID WITHOUT CAUSING TREATMENT-LIMITING ELEVATIONS IN URIC ACID OR GLUCOSE LEVELS OR CAUSING LIVER DAMAGE, BY DOSING ONCE PER DAY IN THE EVENING OR AT	P-IV	SAME AS
6676967	SEP 20,2013	U-548	A METHOD OF REDUCING FLUSH IN AN INDIVIDUAL BEING TREATED FOR A LIPIDEMIC DISORDER AND EFFECTIVELY TREATING THE LIPIDEMIC DISORDER	PIV	Same As
6746691	Sep.20,2013	U-586	AN INTERMEDIATE RELEASE NICOTINIC ACID FORMULATION SUITABLE FOR ORAL ADMINISTRATION ONCE-A-DAY AS A SINGLE DOSE FOR TREATING HYPERLIPIDEMIA WITHOUT CAUSING DRUG-INDUCED HEPATOTOXICITY OR ELEVATIONS IN URIC ACID OR GLUCOSE OR BOTH	P-IV	SAME AS
6818229	FEB 15,2014	Y	Combination use of Niacin and lovastatin	PIV	SAME AS

Exclusivity Data For NDA 20-381

Code/sup	Expiration	Description	Labeling impact

NONE		NONE	NONE

Reference Listed Drug

RLD on the 356(h) form	NIASPAN
NDA Number	20-381
RLD established name	Niacin ER tablets 500 mg, 750 mg, and 1000 mg
Firm	Kos Pharmaceuticals
Currently approved PI	S-013
AP Date	Jan. 31, 2003

Note: The applicant has two separate inserts. At the time of next printing ANDA 76-250 should be combined with ANDA 76-378.

REVIEW OF PROFESSIONAL LABELING CHECK LIST

Established Name	Yes	No	N.A.
Different name than on acceptance to file letter?		X	
Is this product a USP item? If so, USP supplement in which verification was assured. USP 23		X	
Is this name different than that used in the Orange Book?		X	
If not USP, has the product name been proposed in the PF?			X
Error Prevention Analysis			
Has the firm proposed a proprietary name? If yes, complete this subsection.		X	
Do you find the name objectionable? List reasons in FTR, if so. Consider: Misleading? Sounds or looks like another name? USAN stem present? Prefix or Suffix present?			X
Has the name been forwarded to the Labeling and Nomenclature Committee? If so, what were the recommendations? If the name was unacceptable, has the firm been notified?			X
Packaging			
Is this a new packaging configuration, never been approved by an ANDA or NDA? If yes, describe in FTR.	x		
Is this package size mismatched with the recommended dosage? If yes, the Poison Prevention Act may require a CRC.		X	
Does the package proposed have any safety and/or regulatory concerns?		X	
If IV product packaged in syringe, could there be adverse patient outcome if given by direct IV injection?		X	
Conflict between the DOSAGE AND ADMINISTRATION and INDICATIONS sections and the packaging configuration?		X	
Is the strength and/or concentration of the product unsupported by the insert labeling?		X	
Is the color of the container (i.e. the color of the cap of a mydriatic ophthalmic) or cap incorrect?		X	
Individual cartons required? Issues for FTR: Innovator individually cartoned? Light sensitive product which might require cartoning? Must the package insert accompany the product?		X	
Are there any other safety concerns?		X	
Labeling			
Is the name of the drug unclear in print or lacking in prominence? (Name should be the most prominent information on the label).	X		
Has applicant failed to clearly differentiate multiple product strengths?			X
Is the corporate logo larger than 1/3 container label? (No regulation - see ASHP guidelines)		X	
Labeling(continued)	Yes	No	N.A.
Does RLD make special differentiation for this label? (i.e., Pediatric strength vs Adult; Oral Solution vs Concentrate, Warning Statements that might be in red for the NDA)	X	X	
Is the Manufactured by/Distributor statement incorrect or falsely inconsistent between labels and labeling? Is "Jointly Manufactured by...", statement needed?		X	
Failure to describe solid oral dosage form identifying markings in HOW SUPPLIED?		X	
Has the firm failed to adequately support compatibility or stability claims which appear in the insert labeling? Note: Chemist should confirm the data has been adequately supported.		X	
Scoring: Describe scoring configuration of RLD and applicant (page #) in the FTR			
Is the scoring configuration different than the RLD?		X	
Has the firm failed to describe the scoring in the HOW SUPPLIED section?		X	
Inactive Ingredients: (FTR: List page # in application where inactives are listed)			
Does the product contain alcohol? If so, has the accuracy of the statement been confirmed?		X	
Do any of the inactives differ in concentration for this route of administration?		X	
Any adverse effects anticipated from inactives (i.e., benzyl alcohol in neonates)?		X	
Is there a discrepancy in inactives between DESCRIPTION and the composition statement?		X	
Has the term "other ingredients" been used to protect a trade secret? If so, is claim supported?		X	
Failure to list the coloring agents if the composition statement lists e.g., Opacode, Opaspray?			X
Failure to list gelatin, coloring agents, antimicrobials for capsules in DESCRIPTION?			X
Failure to list dyes in imprinting inks? (Coloring agents e.g., iron oxides need not be listed)			X
USP Issues: (FTR: List USP/NDA/ANDA dispensing/storage recommendations)			
Do container recommendations fail to meet or exceed USP/NDA recommendations? If so, are the recommendations supported and is the difference acceptable?		X	
Because of proposed packaging configuration or for any other reason, does this applicant meet fail to meet all of the unprotected conditions of use of referenced by the RLD?		X	
Does USP have labeling recommendations? If any, does ANDA meet them?		X	

Is the product light sensitive? If so, is NDA and/or ANDA in a light resistant container?		X	
Failure of DESCRIPTION to meet USP Description and Solubility information? If so, USP information should be used. However, only include solvents appearing in innovator labeling.		X	
Bioequivalence Issues: (Compare bioequivalency values: insert to study. List Cmax, Tmax, T 1/2 and date study acceptable)			
Insert labeling references a food effect or a no-effect? If so, was a food study done?	x		
Has CLINICAL PHARMACOLOGY been modified? If so, briefly detail where/why.		X	
Patent/Exclusivity Issues?: FTR: Check the Orange Book edition or cumulative supplement for verification of the latest Patent or Exclusivity. List expiration date for all patents, exclusivities, etc. or if none, please state.	X		

NOTES/QUESTIONS TO THE CHEMIST:

FOR THE RECORD:

1. Review based on the labeling of Niaspan; Kos pharm. 20381/S-013app. 1/31/03
2. Patent/ Exclusivities - See above chart
3. Storage Conditions: NDA –RT: ANDA – same USP -N/A
4. Dispensing Recommendations:
   NDA – a tight container with CRC
   ANDA - same
   USP -
5. Scoring: NDA - unscored ANDA - unscored
6. Product Line:
   The innovator markets their product in 500 mg, 750 mg, 1000 mg ER, and a 375 mg (new) bottles of 100s. The 500 mg no longer appears in the orange book as of this review cycle.
   The applicant proposes to market their product 500 mg and 750 mg and related ANDA 76-250 (1000 mg ER) in bottles of 100s with CRC and 250s
7. The tablet/capsule imprint(ings)/embossing(s)/ debossing(s) has/have been accurately described in the HOW SUPPLIED section as required by 21 CFR
8. Inactive Ingredients:
   The listing of inactive ingredients in the DESCRIPTION section of the package insert appears to be consistent with the listing of inactive ingredients found in the statement of components and composition appearing on page 07-2 & 3 vol 1.1 red.
9. Manufactured by Barr.
10. Bio division found generic product to be equivalent to RLD.
11. 76-250 (1000 mg ER) is a separate application to 76-378. Firm has now added a 750 mg strength that is combined with the 500 mg strength. The firm will combine inserts post approval

Date of Review: April 5, 2005 **Date of Submission: Jan. 28, 2005**

cc: ANDA: 76-250
DUP/DIVISION FILE
HFD-613/APayne/JGrace (no cc)
V:firmsam/Barr/lets&rev/76250ap2.Lab Review
Digital signature: Apayne 4/5/05
EDR

4/7/2005 4/5/05

\\Cdsesubogd1\n76250\N_000\2005-01-28\labeling\container.pdf
\\Cdsesubogd1\n76250\N_000\2005-01-28\labeling\brochure.pdf

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 76-250

CHEMISTRY REVIEWS

1. CHEMISTRY REVIEW NO. 1

2. ANDA # **76-250**

3. NAME AND ADDRESS OF APPLICANT

Barr Laboratories, Inc.
Attention: Christine Mundkur
2 Quaker Road
PO Box 2900
Pomona, NY 10970

Tele: (845) 353-8432

4. LEGAL BASIS FOR SUBMISSION

505(j)(2)(A)(vii)(**IV**)

Innovator Product: NIASPAN® XR
Innovator Company: Kos Pharmaceuticals. (NDA 20-381)

	Patent #/Expiration Date	Use Code
Patent	6080428 (05/27/2017) 6129930 (09/20/2013)	U-331 U-354
Exclusivity	None	N/A

5. SUPPLEMENT(s)
N/A

6. PROPRIETARY NAME
None

7. NONPROPRIETARY NAME
Niacin Extended Release Tablets, 1000 mg

8. SUPPLEMENT(s) PROVIDE(s) FOR:
N/A

9. AMENDMENTS AND OTHER DATES:

Submission Date	Submission Type
Barr	
10/02/2001	Original
10/03/2001	NC (form 356h and others)
11/06/2001	NC (ESD/Bioequivalence)
11/21/2001	NC/Bio Study
FDA	
10/03/2001	Accept for Filling
01/09/2001	Labeling review/Deficiency (vol.1.1)

10. PHARMACOLOGICAL CATEGORY: For reducing TC/LDL-C* ". Need
*Form356h says "it is used for the treatment of
provide clarification.

11. Rx or OTC: Rx

12. RELATED IND/NDA/DMF(s)

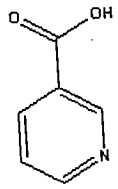
DMF number	DMF type	DMF holder
	II	
Various	III	See Item 38 of this review

13. DOSAGE FORM: Extended Release Tablets

14. POTENCY: 1000 mg

15. CHEMICAL NAME AND STRUCTURE

Niacin [59-67-6] $C_6H_5NO_2$ 123.111



16. RECORDS AND REPORTS

N/A

17. COMMENTS

EERs: Pending
DMF Status: Adequate/IR (01/29/02)
Labeling review: Deficient (01/09/2002)
Bio-review: (under review)
Micro: N/A
MV/DP: Issued with this review.
CMC: Deficient/MINOR. Deficiencies under item 38.

18. CONCLUSIONS AND RECOMMENDATIONS
Not Approvable (Minor)

19. REVIEWER:
Bing Cai, Ph.D.

DATE COMPLETED:
01/30/01

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confidential commercial

information from

CHEMISTRY REVIEW #1

8. [redacted]

B. In addition to responding to the deficiencies presented above, please note and acknowledge the following comments in your response:

1. All facilities referenced in the ANDA should have a satisfactory compliance evaluation at the time of approval. We have requested an evaluation from the Office of Compliance.

2. Your Bioequivalence information is pending review. Deficiencies, if any, will be communicated separately.

3. Labeling deficiencies will also need to be addressed in your reply.

4. We require an acceptable Methods Validation to support the ANDA and we are currently scheduling the study. Please provide samples promptly when contacted. Please also provide a commitment to work with us to expeditiously resolve any deficiencies from the Methods Validation study if the ANDA is approved prior to its completion.

5. Please provide any additional long term stability data that may be available.

6. You have not provided the Paragraph IV information specified in our acknowledgement letter dated November 26, 2001.

Sincerely yours,

Paul Schwartz 2/19/02

Rashmikant M. Patel, Ph.D.
Director
Division of Chemistry I
Office of Generic Drugs
Center for Drug Evaluation and Research

cc: ANDA 76-250
DUP
Field Copy
Division File

Endorsements:

HFD-625/B.Cai/01/31/02
HFD-625/M. Smela/02/15/02
HFD-617/M. Dillahunt, PM/02/15/02
V:\FIRMSAM\BARR\LTRS&REV\76250cr1.bbc.doc
F/T by: gp/02/19/02

2/19/02 for M Smela 2/19/02
M Dillahunt 2/19/02

NOT APPROVABLE MINOR DEFICIENCIES

APPEARS THIS WAY
ON ORIGINAL

1. CHEMISTRY REVIEW NO. 2 2. ANDA # **76-250**

3. NAME AND ADDRESS OF APPLICANT

Barr Laboratories, Inc.
Attention: Christine Mundkur
2 Quaker Road, PO Box 2900
Pomona, NY 10970

Tele: (845) 353-8432

4. LEGAL BASIS FOR SUBMISSION

505(j)(2)(A)(vii)(**IV**)

Innovator Product: NIASPAN® XR
Innovator Company: KOS Pharmaceuticals. (NDA 20-381)

	Patent #/Expiration Date	Use Code
Patent	6080428 (05/27/2017) 6129930 (09/20/2013)	U-331 U-354
Exclusivity	None	N/A

Information regarding Paragraph IV requirement have been amended to this ANDA.

5. SUPPLEMENT(s): N/A

6. PROPRIETARY NAME: None

7. NONPROPRIETARY NAME: Niacin Extended Release Tablets

8. SUPPLEMENT(s) PROVIDE(s) FOR: N/A

9. AMENDMENTS AND OTHER DATES:

Submission Date	Submission Type
Barr	
10/02/2001	Original
03/04/2002	Patent Amendment (Paragraph IV Letter)
03/22/2002	Patent Amendment (Paragraph IV/litigation)
03/25/2002	**First Minor Amendment***
05/17/2002	Minor Amendment/Bio
FDA	
11/26/2001	Acknowledgment/Accept for Filling/10/03/01
01/09/2001	Labeling review/Deficiency (Vol.1.1)
02/20/2002	NA/Minor, CMC and labeling (Vol.1.1)
04/29/2002	Labeling/Acceptable, Pending FPL (Vol. 2.1)
05/03/2002	Bio deficiency letter (Vol 1.1)
08/12/2002	Bio letter faxed

*Subject of this review.

10. PHARMACOLOGICAL CATEGORY:
An adjunct to diet for treating hyperlipidemia*
(*See amendment dated 03/25/02)

11. Rx or OTC: Rx

12. RELATED IND/NDA/DMF(s)

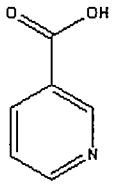
DMF number	DMF type	DMF holder
[redacted]	II	[redacted]
Various	III	See Item 38 of this review

13. DOSAGE FORM: Extended Release Tablets

14. POTENCY: 1000 mg

15. CHEMICAL NAME AND STRUCTURE

Niacin [*59-67-6*] $C_6H_5NO_2$ 123.111



16. RECORDS AND REPORTS: N/A

17. COMMENTS

EERs: Pending (05/14/2002)
DMF [redacted] Status: Adequate (05/17/2002)
Labeling review: Pending for FPL (04/29/2002)
Bio-review: Adequate (08/01/2002)
Micro: N/A
MV/DP: Pending.
CMC: Deficient/NA, Minor

18. CONCLUSIONS AND RECOMMENDATIONS
Not Approvable, NA Minor

19. REVIEWER:
Bing Cai, Ph.D.

DATE COMPLETED:
05/17/2002
DATE REVISED:
08/07/2002

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information from

CHEMISTRY REVIEW #2

cc: ANDA 76-250
DUP
Field Copy
Division File

Endorsements:

HFD-625/B.Cai/05/17/02/08/06/02 9/26/02
HFD-625/S. Liu/08/26/02 S.H. Liu 9/27/02
HFD-617/W. Pamphile PM/09/25/02 9/30/02
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F/T by: gp/09/25/02

APPEARS THIS WAY
ON ORIGINAL

1. CHEMISTRY REVIEW NO. 3 2. ANDA # **76-250**

3. NAME AND ADDRESS OF APPLICANT

Barr Laboratories, Inc.
Attention: Christine Mundkur
2 Quaker Road, PO Box 2900
Pomona, NY 10970

Tele: (845) 353-8432

4. LEGAL BASIS FOR SUBMISSION

505(j)(2)(A)(vii)(**IV**)

Innovator Product: NIASPAN® XR
Innovator Company: KOS Pharmaceuticals. (NDA 20-381)

	Patent #/Expiration Date	Use Code
Patent	6080428 (05/27/2017) 6129930 (09/20/2013)	U-331 U-354
Exclusivity	None	N/A

Information regarding Paragraph IV requirement have been amended to this ANDA.

5. SUPPLEMENT(s): N/A

6. PROPRIETARY NAME: None

7. NONPROPRIETARY NAME: Niacin Extended Release Tablets

8. SUPPLEMENT(s) PROVIDE(s) FOR: N/A

9. AMENDMENTS AND OTHER DATES:

Barr	
Submission Date	Submission Type
10/02/2001	Original
03/04/2002	Patent Amendment (Paragraph IV Letter)
03/22/2002	Patent Amendment (Paragraph IV/litigation)
03/25/2002	First Minor Amendment*
05/17/2002	Minor Amendment/Bio
08/29/2002	Patent Amendment
08/30/2002	Patent Amendment
12/09/2002	Patent Amendment
12/13/2002	**Minor Amendment***
02/24/2003	**Telephone Amendment***

*Subject of this review.

FDA	
Submission Date	Submission Type
11/26/2001	Acknowledgment/Accept for Filling/10/03/01
01/09/2001	Labeling review/Deficiency (Vol.1.1)
02/20/2002	NA/Minor, CMC and labeling (Vol.1.1)
04/29/2002	Labeling/Acceptable, Pending FPL (Vol. 2.1)
05/03/2002	Bio deficiency letter (Vol 1.1)
08/12/2002	Bio letter faxed
10/07/2002	NA Minor/letter issued
02/05/2003	T-Con

10. PHARMACOLOGICAL CATEGORY:
An adjunct to diet for treating hyperlipidemia

11. Rx or OTC: Rx

12. RELATED IND/NDA/DMF(s)

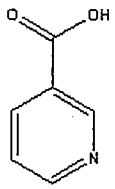
DMF number	DMF type	DMF holder
[redacted]	II	[redacted]
Various	III	See Item 38 of this review

13. DOSAGE FORM: Extended Release Tablets

14. POTENCY: 1000 mg

15. CHEMICAL NAME AND STRUCTURE

Niacin [*59-67-6*] $C_6H_5NO_2$ 123.111



16. RECORDS AND REPORTS: N/A

17. COMMENTS

EERs: Acceptable (10/17/2002)
DMF [redacted]) Status: Adequate (04/08/2003)
Labeling: Tentative Approval Summary (04/29/2002)
Bio-review: Acceptable (1/28/2003, 03/31/03)
Micro: N/A
MV/DP: **Pending.**
CMC: Satisfactory

18. CONCLUSIONS AND RECOMMENDATIONS
Approvable. (Pending for MV)

19. REVIEWER:
Bing Cai, Ph.D.

DATE COMPLETED:
12/31/2002
DATE REVISED:
03/03/2003, 04/08/03

APPEARS THIS WAY
ON ORIGINAL

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information from

CHEMISTRY REVIEW #3

cc: ANDA 76-250
DUP
Field Copy
Division File

Endorsements:

HFD-625/B.Cai/12/31/02, 03/03/03, 04/08/03
HFD-625/S. Liu/ S.H.Liu 4/9/03
HFD-617/W. Pamphile PM/ ~~dtf~~ 4/17/03
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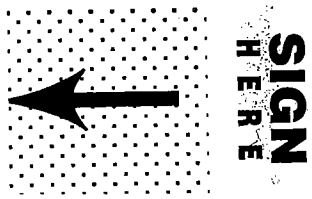
F/T by:

4/4/03

APPEARS THIS WAY
ON ORIGINAL



ANDA 76-250

NIACIN Extended Release Tablets 1000 mg

Barr Laboratories, Inc.
Pomona, New York

Bing Cai, Ph. D.

Division of Chemistry I
Office of Generic Drugs

Table of Contents

Chemistry Review Data Sheet

1. ANDA 76-250 (First Generic Drug)

2. REVIEW #: 4 (TA to Final Approval)

3. REVIEW DATE: 1/14/05

4. REVIEWER: Bing Cai, Ph.D.

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
Barr	
Original	10/02/2001
First Minor Amendment	03/25/2002
Minor Amendment/Bio	05/17/2002
Minor Amendment	12/13/2002
Telephone Amendment	02/24/2003
FDA	
Acceptable for Filling	11/26/01
TA	05/09/2003
T-con	**02/18/05**
T-con	**03/03/05**
T-con	**03/11/05**

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Minor Amendment (TA to Final AP)	January 28, 2005
Telephone Amendment	March 4, 2005
Telephone Amendment	March 11, 2005

7. NAME & ADDRESS OF APPLICANT:

Name:	Barr Laboratories, Inc.
Address:	2 Quaker Road, P.O. Box 2900, Pomona, NY 10970
Representative:	Nicholas Tantillo
Telephone:	201-930-3650

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: N/A
b) Non-Proprietary Name (USAN): Niacin

9. LEGAL BASIS FOR SUBMISSION: 505 j

505(j)(2)(A)(vii)(**IV**)

Innovator Product: NIASPAN® XR Tablets, 500 mg, 750 mg and 1000 mg
Innovator Company: Kos Pharmaceuticals. (NDA 20-381)

10. PHARMACOL. CATEGORY:

Reduction of cholesterol ; Treatment of high serum

11. DOSAGE FORM: Tablet, Extended Release

12. STRENGTH/POTENCY: 1000 mg

13. ROUTE OF ADMINISTRATION: Oral

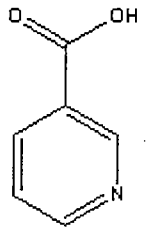
14. Rx/OTC DISPENSED: _x__Rx ___OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

_____SPOTS product – Form Completed

___x___Not a SPOTS product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:



Niacin [*59-67-6*] $C_6H_5NO_2$ 123.111

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
	II			7	Adequate		Adequate per 05/09/03 when it was TAed*
	III			4	N/A		
	III			4	N/A		
	III			4	N/A		
	III			4	N/A		
	III			4	N/A		Newly added
	III			4	N/A		
	III			4	N/A		
	III			4	N/A		
	III			4	N/A		
	III			4	N/A		

* DMF is not reviewed since this ANDA has been TAed.

[1] Action codes for DMF Table:
1 – DMF Reviewed.
Other codes indicate why the DMF was not reviewed, as follows:
2 –Type 1 DMF
3 – Reviewed previously and no revision since last review
4 – Sufficient information in application
5 – Authority to reference not granted
6 – DMF not available
7 – Other (explain under "Comments")

[2] Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
Barr' ANDA Application	ANDA 76-250	Niacin ER Tablets, 1000 mg

18. STATUS:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	Note
Microbiology	N/A	--	--
EES	Acceptable per 02/23/05	--	J.D. Ambrogio
Methods Validation	Not required	--	--
Labeling	Acceptable	4/7/05	A. Payne
Bioequivalence	Satisfactory	1/28/03	H. Nguyen
EA	N/A	--	
Radiopharmaceutical	N/A	--	

19. ORDER OF REVIEW

The application submission(s) covered by this review was taken in the date order of receipt. _x___ Yes _____ No If no, explain reason(s) below:

APPEARS THIS WAY
ON ORIGINAL

The Chemistry Review for ANDA 76-250

The Executive Summary

I. Recommendations:

A. Recommendation and Conclusion on Approvability:
The ANDA is approvable.

B. **Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable:** No post-approval commitments are necessary as a condition of approval for this ANDA.

II. Summary of Chemistry Assessments

Request from TA to final approval: In Barr's patent amendment dated December 9,2002, they informed the FDA that KOS, the NDA holder and patent owner, received notice relating to U.S. Patent No 6,406,715 (the '715 patent) on September 30,2002, and that KOS filed a complaint in the U.S. District Court, Southern District of New York. Barr's notice relating to the '715 patent forms the basis for a 30-month period that began on September 30,2002 and will end on March 30,2005. ANDA 76-250 will be eligible for final approval when this 30-month period ends on March 30, 2005.

A. Description of the Drug Product(s) and Drug Substance(s)

- The drug product, Niacin Extended Release Tablets, 1000 mg is labeled for oral use. Barr's drug products are packaged in 100's or 250's HDPE bottles which meet the requirement as the well-closed containers.

- There is no USP monograph for Niacin ER Tablets. Barr has developed their own in-house —— Assay/Impurities and drug release —— methods. These analytical methods are identical to those methods used in ANDA 76-378 (1000 mg).

- [ ]

- The drug substance, Niacin USP or 3-pyridinecarboxylic acid [*59-67-6]* has a USP Monograph. ———— is the current DS supplier for Barr. In ANDA 76-250, Barr cited the results from the DMF holder, which indicate that the NIACIN does not ——

[ ]

Barr's DS specifications comply with the specifications established by the USP. In

addition, Barr has added an acceptance criteria for ——— as an additional drug substance testing. They are adequate.

- Barr's impurity specifications for drug substance and drug product have been revised to meet the requirement per ICH recommendation at this cycle.

B. Description of How the Drug Product is Intended to be Used

- The drug product are packaged in 100's CRC and 250's bottles. The daily dose for the drug product is up to 2000 mg .

  (MDD= 2000 mg)

- The expiration dating period for the drug product is 24 months and the recommended storage conditions are 1) Protect from light and 2) Store at controlled room temperature ———

C. Basis for Approvability or Not-Approval Recommendation

The ANDA is approvable.

III. Administrative

A. Reviewer's Signature: for RSpandel 4/12/05

Bing Cai, Ph.D.

B. Endorsement Block

Endorsements (Draft and Final with Dates): for RSpandel 4/12/05
HFD-620 /B. Cai, Ph.D/02/14/05, 03/14/05
HFD-620/A. Mueller, Ph.D./ 4-12-05
HFD-620/PM, B. Danso, R. Ph./4-12-05

F/T by

V:\FIRMSAM\BARR\LTRS&REV\76250cr4.bbc.doc

C. CC Block

ANDA 76-250
ANDA DUP
DIV FILE
Field Copy

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confidential commercial

information from

CHEMISTRY REVIEW #4

cc: ANDA 76-250
ANDA DUP
DIV FILE
Field Copy

Endorsements (Draft and Final with Dates):

HFD-620 /B. Cai, Ph.D/01/14/05, 03/14//05

HFD-620/A. Mueller, Ph.D./

HFD-620/B. Danso, Pharm.D./

F/T by:

V:\FIRMSAM\BARR\LTRS&REV\76250cr4.bbc.doc

TYPE OF LETTER:

APPEARS THIS WAY
ON ORIGINAL

APPROVAL SUMMARY PACKAGE

ANDA NUMBER: 76-250

FIRM: Barr Laboratories, Inc.

DOSAGE FORM: Tablets

STRENGTH: 1000 mg

DRUG: Niacin Extended Release Tablets

cGMP STATEMENT/EER UPDATED STATUS: *Acceptable 10/17/2002*

BIO STUDY: *Acceptable per 01/28/03 then reconfirmed on 03/31/03 (Please also refer to ANDA 76-378)*

METHODS VALIDATION - (DESCRIPTION OF DOSAGE FORM SAME AS FIRM'S):
Pending

STABILITY - ARE CONTAINERS USED IN STUDY IDENTICAL TO THOSE IN CONTAINER SECTION?

Containers used in the stability studies are identical to those listed in container section.

Expiration dating period is 24 months for the drug product.

LABELING: Acceptable (TA) *per 04/29/02*

STERILIZATION VALIDATION (IF APPLICABLE): N/A

SIZE OF BIO BATCH - (FIRM'S SOURCE OF NDS O.K.?):

	Bio/Stability Batch	Production
Lot#	202141002R	--
Batch Size	[redacted] tablets	[redacted] tablets

NDS Source	Information
DMF#	[redacted]
Manufacturer	[redacted]
DMF last update	Last amendment: 03/18/03
DMF status	Last review: 04/08/03

SIZE OF STABILITY BATCHES - (IF DIFFERENT FROM BIO BATCH WERE THEY MANUFACTURED VIA SAME PROCESS?)

	Bio/Stability Batch	Production
Lot#	202141002R	--
Batch Size	[redacted] tablets	[redacted] tablets

PROPOSED PRODUCTION BATCH - MANUFACTURING PROCESS THE SAME AS BIO/STABILITY?

The proposed production batch size is the same as bio/stability batches.

	Bio/Stability Batch	Production
Lot#	202141002R	--
Batch Size	[redacted] tablets	[redacted] tablets

Bing Cai. Ph.D/04/08/03
Review Chemist

S. H. Liu 4/9/03

Shing Liu, Ph.D
Team Leader

Division of Chemistry I
OGD/CDER

APPEARS THIS WAY
ON ORIGINAL

cc: ANDA 76-250
Division File
Field Copy

4/8/03

Endorsements:
HFD-620/BCai/04/08/03
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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 76-250

BIOEQUIVALENCE REVIEWS

Niacin Extended Release Tablets
1000 mg
ANDA 76-250
Reviewer: Chandra S. Chaurasia

Barr Laboratories, Inc.
Pomona, NY 10970
Submission Date:
10/02/2001

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Review of Two Bioequivalence Studies and Dissolution Data

Introduction

First Generic: Yes

Type of Submission: Original

Contents of Submission:

1. Fasting and non-fasting studies.
2. Dissolution data.

Indication: Niaspan® is indicated as an adjunct to diet for reduction of elevated total cholesterol, low-density lipoprotein cholesterol and triglyceride levels, and to increase high-density lipoprotein cholesterol in patients with primary hypercholesterolemia and mixed dyslipidemia.

Reference Listed Drug: Niaspan® (Niacin, NDA 20381, July 28, 1997) tablets are available as 375 mg, 500 mg, 750 mg and 1000 extended release tablets manufactured by KOS Pharmaceutical. The Orange Book (Electronic 2002) lists each of these Niaspan® extended release tablets as the reference listed drugs. In addition, the Orange Book also lists NIASPAN TITRATION STARTER PACK containing Niacin 375 mg, 500 mg and 750 mg extended-release tablets under the same NDA 20831.

***Note**: Single-dose bioavailability studies have demonstrated that NIASPAN tablet strengths are not interchangeable.*

Pharmacokinetics/Metabolism

Absorption

Niacin is rapidly and extensively absorbed (at least 60 to 76% of dose) when administered orally.

Metabolism

The pharmacokinetic profile of niacin is complicated due to rapid and extensive first-pass metabolism, which is species and dose-rate specific. In humans, one pathway is through a simple conjugation step with glycine to form nicotinuric acid (NUA). NUA is

then excreted in the urine, although there may be a small amount of reversible metabolism back to niacin. The other pathway results in the formation of nicotinamide adenine dinucleotide (NAD). It is unclear whether nicotinamide is formed as a precursor to, or following the synthesis of, NAD. Nicotinamide is further metabolized to at least N-methylnicotinamide (MNA) and nicotinamide-N-oxide (NNO). MNA is further metabolized to two other compounds, N-methyl-2-pyridone-5- carboxamide and N-methyl-4-pyridone-5-carboxamide. At the doses used to treat hyperlipidemia, these metabolic pathways are saturable, which explains the nonlinear relationship between niacin dose and plasma concentrations following multiple-dose NIASPAN administration.

Nicotinamide does not have hypolipidemic activity; the activity of the other metabolites is unknown.

Elimination

Niacin and its metabolites are rapidly eliminated in the urine. Following single and multiple doses, approximately 60 to 76% of the niacin dose administered as NIASPAN was recovered in urine as niacin and metabolites; up to 12% was recovered as unchanged niacin after multiple dosing. The ratio of metabolites recovered in the urine was dependent on the dose administered.

Gender

Steady-state plasma concentrations of niacin and metabolites after administration of NIASPAN are generally higher in women than in men, with the magnitude of the difference varying with dose and metabolite. Recovery of niacin and metabolites in urine, however, is generally similar for men and women, indicating that absorption is similar for both genders.

DOSAGE AND ADMINISTRATION

To maximize bioavailability and reduce the risk of gastrointestinal (GI) upset, Niaspan should be taken at bedtime after a low-fat snack. Per the RLD labeling, therapy with Niaspan must be initiated at 500 mg.

The recommended maintenance dose is 1000mg (two 500mg tablets) to 2000mg (two 1000mg tablets or four 500mg tablets) once daily at bedtime.

History:

The Division of Bioequivalence has reviewed three control documents (OGD 00-329, ————————, Aug 04, 2000, OGD#00-363, Barr Laboratories, August 30, 2000 and OGD#01-342, ———————— June 27, 2001) on this drug product. Per the "*Guidance for Industry: Bioavailability and Bioequivalence Studies for Orally*

Administered Drug Products – General Considerations", issued in October 2000, the Division has made the following recommendations:

1. To conduct the following studies to demonstrate bioequivalence of generic niacin extended release tablets, 375 mg, 500 mg, 750 mg, and 1000 mg:

   (a) Single-dose, replicate, fasting studies comparing each strength of the test and reference drug products. The reference product label states that single dose bioavailability studies have demonstrated that Niaspan® tablet strengths are not interchangeable.
   (b) A single-dose, non-fasting, non-replicate study comparing the 1000 mg strength of the test and reference drug product.
   (c) It is acceptable to dose the drug in the morning as is customary for pharmacokinetic studies.

Reviewer's Note: *Currently, the DBE recommends 2-way crossover, single-dose fasting study. The firm has an option to use replicate design. However, the statistical analysis will be based on average bioequivalence.*

2. To measure plasma concentrations of the parent drug and the metabolite, nicotinuric acid for bioequivalence studies of niacin extended release tablets. If niacin cannot be reliably measured using a selective and sensitive analytical method, then nicotinuric acid data should be subjected to a confidence interval approach for bioequivalence assessment. If niacin can be reliably measured, niacin data should be subjected to a confidence interval approach for bioequivalence assessment. Plasma concentration data of niacin and nicotinuric acid should be submitted to the Agency.

3. For data analysis, DBE continues to use the average BE criterion to compare bioavailability measures for replicate and non-replicate BE studies.

Protocol No. 10016214: The Relative Bioavailability of Two Niacin Formulations under Fasting Conditions.

Study Information

Clinical Facility: [redacted]
Principal Investigator: [redacted] M.D.
Clinical Study Dates: Period I: February 24, 2001, Period II: March 03, 2001
Period III: March 10, 2001 and Period IV: March 17, 2001
(Vol. 1.7, pp. 6-2986)
Analytical Facility: [redacted] (per pp. 6-473, Vol. 1.1)
Chief Executive Officer: [redacted] (per pp. 6-473, Vol. 1.1)
Analytical Study Dates: 06/01/01 to 07/23/01 (Vol. 1.4, pp. 6-2048).
Storage Period: 150 days

Treatment Information

Treatment ID:	A	B
Test or Reference:	T	R
Product Name:	Niacin Extended Release Tablets	Niaspan ® Tablets
Manufacturer:	Barr Laboratories, Inc.	KOS Pharmaceuticals, Inc.
Manufacturing Date:	01/18/01	N/A
Expiration Date:	N/A	02/2003
ANDA Batch Size:	———	N/A
Batch/Lot Number:	202141002R	0005300007
Potency:	99.6%	101.5%
Content Uniformity:	99.4% (RSD 0.8%)	101.5 (RSD 0.3%)
Strength:	1000 mg	1000 mg
Dosage Form:	Tablet	Tablet
Dose Administered:	1000 mg (1x1000 mg)	1000 mg (1x1000 mg)
Study Condition:	Fasting	Fasting
Length of Fasting:	Overnight	Overnight

RANDOMIZATION		**DESIGN**	
Randomized:	Y	**Design Type:**	crossover
No. of Sequences:	2	**Replicated Treatment**	Y
No. of Periods:	4	**Balanced:**	Y
No. of Treatments:	2	**Washout Period:**	7 days

Randomization Scheme: **ABAB**: 1,3,5,7,9,12,14,15,18,20,22,23,25,28,30,32,33,36
BABA 2,4,6,8,10,11,13,16,17,19,21,24,26,27,29,31,34,35

DOSING		**SUBJECTS**	
Single or Multiple Dose:	Single	**IRB Approval:**	Y
Steady State:	N	**Informed Consent Obtained:**	Y
Volume of Liquid Intake:	240 mL	**No. of Subjects Enrolled:**	36
Route of Administration:	Oral	**No. of Subjects Completing:**	32*
Dosing Interval:	N/A	**No. of Subjects Plasma Analyzed:**	32**
		No. of Subjects Statistical Analyses Performed:	32
Number of Doses:	N/A	**No. of Dropouts:**	Four*
Loading Dose:	N/A	**Sex(es) Included:**	Males and Females†
Steady State Dose Time:	N/A	**Healthy Volunteers Only:**	Y
Length of Infusion:	N/A	**No. of Adverse Events:**	56

*Subject #30 withdrew from the study participation prior to Period I (Test) dosing due to abdominal discomfort. Sub # 3 voluntarily withdrew from study prior to Period II (Ref) for personal reasons. Sub #15 voluntarily withdrew from the study 35 hours after Period I (Test) dosing due to an adverse event (fainting). Sub #20 was withdrawn from the study by the Investigator at Period II (Ref) due to a positive cocaine test.

**Sub #27 experienced emesis approximately 6 hours after dosing Period II (Test). Her samples for this period were not analyzed. She completed Periods I, III and IV of the study without further incident and her samples for these periods were analyzed. Sub #5 experienced emesis approximately 18 hours after dosing Period IV (Ref) and in accordance with the protocol was withdrawn from this period of the study. Her samples for this period were not analyzed. She completed Periods I, II and III without further incident, and her samples for these periods were analyzed.

†**Demographic Data:**

No of Subj	Race /Ethnic Group						Sex		Age Group (Yr.)						Height (in)		Weight (lbs.)	
Total	A¶	B¶	C¶	H¶	NA¶	OT¶	M	F	Mean*	Range§ R1	R2	R3	R4	R5	Mean	Range	Mean	Range
36	2	23	6	4	1		23	13	31.6	0	27	9	0	0	66.7	61-74	172.4	115-320

¶ A: Asian, B: Black, C: Caucasian, H: Hispanic, NA: Native American, OT: Other (e.g., biracial)
§ R1: <18, R2: 18-40, R3: 41-64, R4: 65-75, R5: >75

Blood Sampling: One x 7 mL each before dosing (0-time) and at 0.5, 1,1.5, 2, 2.5, 3, 4, 5, 6, 8, 10, 12, 15, 18, and 24 hours collected in vacutainers containing lithium heparin. The blood was centrifuged at 2500-2700 rpm for 15 minutes at 4 °C, and all plasma samples were stored at –20 °C, pending assay.

Dietary Restrictions: No alcohol-, xanthine-, containing beverages/foods for 24 hrs pre-dose and throughout sample collection period. No water 1 hr before/after dosing. Fasted overnight pre-dose and 4 hrs post-dose.

Activity Restrictions: Subjects remained ambulatory or seated upright for the first 4 hours post-dose, except when warranted by medical events. No strenuous activity during the housing period.

Drug Restrictions: No prescription drugs for a period of 14 days and OTC products or any vitamin/herbal products containing niacin within 72 hours prior to dosing.

Female Subjects: Females of child bearing potential must be prepared to abstain from sexual intercourse or use a reliable method of contraception during the study. Females who are pregnant, breast-feeding or likely to become pregnant during the study will be excluded.

Study Results

1) Clinical

Adverse Events:

During the study, 89 adverse events (47 Test and 42 Ref) were reported by 23 of the 36 subjects. Thirty-three of these AEs were found unrelated to the study drugs. Fifty-six of the drug-related adverse events (Test: 29, Ref: 27) are summarized in the table below:

Adverse Events	No of Adv. Events	Test	Ref	Severity	Resolution	Relationship to study drugs
Flushing	11	6	5	Mild	Spontaneous	Possible/Probable
Headache	14	9	5	Mild	Spontaneous	Possible/Probable
Nausea	6	3	3	Mild	Spontaneous	Possible/Probable
Emesis	1	1	0	Mild	Spontaneous	Possible
Emesis*	1	0	1	Mild	Treatment (BC Powder)*	Possible
Dizzy	6	1	5	Mild	Spontaneous	Remote/Possible
Diarrhea	3	1	2	Mild	Spontaneous	Possible
Flatulence/stomach discomfort	6	3	3	Mild	Spontaneous/Treatment (Pepto Bismol)	Remote/Possible
Feeling Hot	1	1	0	Mild	Spontaneous	Remote
Rash	3	2	1	N/A	Spontaneous	Remote
Tachycardia	1	0	1	Mild	Spontaneous	Remote
Pustule, Right arm	1	1	0	Mild	Spontaneous	Remote
Tingling Sensation	2	1	1	Mild	Spontaneous	Remote

**Subject 5 Period IV. Drug indicated as BC powder in the Case Report Form section (Vol. 1.7, pp. 6-3280) of the submission. Active ingredient for this drug has not been provided. The reviewer notes that subject 5 was withdrawn from the study.*

Protocol Deviations: None other than minor sampling deviations

2) Analytical (Not to be released under FOI)

Analytical Method Validation

Analytes: Niacin and Nicotinuric acid

Assay Method: ———

Matrix: plasma

Assay Validation – Pre-Study Analyte: Niacin			
QC Conc. (ng/mL)	LQC: 50.0	MQC: 250.0	HQC: 1400
Intra day Precision (%CV)			
Intra day Accuracy (% accuracy)			
Inter day Precision (%CV)			
Inter day Accuracy (% accuracy)			
Stability in Plasma			
Room Temp.	24 hours		
In Process stability	72 hours at room temp		
Freeze-Thaw Cycles	Stable after 3 freeze-thaw cycles		
Long-term storage at –20 ºC	78 days (addendum, Vol. 1.1, pp. 6-388)		
Regression	weighted ($1/x^2$) linear regression		
Linearity (average of r^2 values)			
Linearity range (ng/mL)			
Limit of Quantitation/Sensitivity (ng/mL)	Lower limit of Quantitation (LLOQ):		
Mean % recovery			
Recovery of Internal Standard			
Specificity	No interfering peaks		
Dilution Integrity			

Assay Validation – Within Study Analyte: Niacin	
Calibration Curve Standard Conc. (ng/mL)	
Inter day Precision (%CV)	
Inter day Accuracy (% Accuracy)	
r^2 value of representative calibration curve	
Linearity Range (ng/mL)	

Assay Validation – Pre-Study Analyte: Nicotinuric Acid			
QC Conc. (ng/mL)	LQC: 50.0	MQC: 250.0	HQC: 1400
Intra day Precision (%CV)			
Intra day Accuracy (% accuracy)			
Inter day Precision (%CV)			
Inter day Accuracy (% accuracy)			
Stability in Plasma			
Room Temp.	24 hours		
In Process stability	72 hours at room temp		
Freeze-Thaw Cycles	Stable after 3 freeze-thaw cycles		
Long-term storage at –20 ºC	78 days (addendum, Vol. 1.1, pp. 6-389)		
Regression	weighted ($1/x^2$) linear regression		
Linearity (average of r^2 values)			
Linearity range (ng/mL)			
Limit of Quantitation/Sensitivity (ng/mL)	Lower limit of Quantitation (LLOQ):		

Mean % recovery	
Recovery of Internal Standard	
Specificity	No interfering peaks
Dilution Integrity	

Assay Validation – Within Study Analyte: Nicotinuric Acid	
Calibration Curve Standard Conc. (ng/mL)	
Inter day Precision (%CV)	
Inter day Accuracy (% Accuracy)	
r^2 value of representative calibration curve	
Linearity Range (ng/mL)	

Analytical Repeats:

A total of 70 out of 2014 (3.5%) samples were repeated due to analytical reasons as described below:

Analytical Reasons	No of samples repeated
Values above the quantifiable limit	48
Unacceptable chromatography	16
High internal standard	2
Improper integration	1
Peak at zero hour	1
Low internal standard	1
Laboratory accident	1

Comments on Analytical Methodology:

Fifteen niacin, 21 nicotinuric acid and 12 niacin/nicotinuric acid sample concentrations were outside the calibration range

Based on the firm's reported results, analyses for plasma niacin and nicotinuric acid for fasting study were completed on July 23, 2001. Considering the clinical study initiation day on February 24, 2001, the overall storage period for the plasma niacin and nicotinuric acid samples is 150 days. The firm has submitted long-term frozen stability study covering a period of 78 days only. Analytical method validation for niacin and nicotinuric acid for the assay of plasma samples obtained in the fasting study is therefore incomplete.

3) Pharmacokinetic and Statistical Analysis:

Mean Plasma Concentrations: Niacin: Table 1, Nicotinuric Acid: Table 4
Pharmacokinetics Measures: Niacin: Tables 2 and 3, Nicotinuric Acid: Tables 5 and 6

Table 1. Fasting Single-Dose In Vivo Bioequivalence Study # 10016214 Arithmetic Mean Plasma Niacin Concentrations [ng/mL]* ((± SD)) Vs. Time (N = 32)

Time(hours)	Test Mean (A)	Test SD	Ref Mean (B)	Ref SD	A/B Ratio
0.000	0.00	0.00	0.00	0.00	-
0.500	567.43	1016.55	477.12	1024.72	1.19
1.00	637.10	1694.27	383.30	660.89	1.66
1.50	475.60	991.71	452.17	1019.12	1.05
2.00	383.18	553.46	262.78	667.46	1.46
2.50	286.46	532.67	293.86	604.93	0.97
3.00	156.54	222.73	131.00	157.60	1.19
4.00	96.45	145.29	174.79	403.52	0.55
5.00	68.60	106.25	71.71	113.29	0.96
6.00	59.80	167.50	34.99	42.59	1.71
8.00	16.85	19.25	52.31	110.63	0.32
10.0	19.71	21.51	33.74	35.86	0.58
12.0	22.43	30.86	20.68	27.55	1.08
15.0	9.96	19.92	4.99	12.34	2.00
18.0	4.87	12.63	2.05	7.90	2.38
24.0	0.48	3.59	0.00	0.00	-

Table 2. Fasting Single-Dose In Vivo Bioequivalence Study # 10016214 Arithmetic Means (±SD) of Pharmacokinetic Parameters for Niacin (N = 32)

PK Measures	Test (A)	Reference (B)
AUCt [ng•hr/mL]	1507.25 ± 1990.02	1431.59 ± 1714.92
AUCi [ng•hr/mL]	1540.04 ± 845.15	1961.62 ± 2446.80
Cmax [ng/mL]	977.32 ± 1601.90	872.54 ± 1108.58
tmax [hr]	1.71 ± 1.45	1.80 ± 1.66
k_{el} [1/hr]	0.50 ± 0.59	0.36 ± 0.33
t½ [hr]	4.16 ± 4.55	3.83 ± 3.56

Table 3. Summary Statistics for Niacin Single-Dose In Vivo Bioequivalence Study # 10016214 Under Fasting Conditions, N = 32

PK Measures*	Geometric Mean		Within Sub Variability		Ratio of Within-Subj Variability	A/B	90% CI
	Test (A)	Ref (B)	Test	Ref	T/R		
Ln AUCt (ng•hr/mL)	1046.36	1047.21	0.3977	0.5404	0.74	1.00	87.34-114.31
Ln AUCi (ng•hr/mL)	1202.07	1268.10	0.2928	0.5575	0.53	0.94	75.46-118.78
Ln Cmax (ng/mL)	583.46	561.92	0.6363	0.6297	1.01	1.04	86.25-124.99

**geometric mean values for ln-transformed data reported*

Table 4. Fasting Single-Dose In Vivo Bioequivalence Study # 10016214 Arithmetic Mean Plasma Nicotinuric Acid Concentrations [ng/mL]* ((± SD)) Vs. Time (N = 32)

Time(hours)	Test Mean (A)	Test SD	Ref Mean (B)	Ref SD	A/B Ratio
0.000	0.00	0.00	0.00	0.000	-
0.500	501.71	406.22	429.50	350.47	1.17
1.00	781.52	462.03	786.81	539.19	0.99
1.50	937.94	525.23	837.68	489.76	1.12
2.00	828.79	537.98	754.94	514.10	1.10
2.50	741.49	442.84	696.87	502.10	1.06
3.00	618.99	441.35	587.95	446.50	1.05
4.00	419.28	359.37	491.81	422.40	0.85
5.00	292.59	291.54	299.48	283.30	0.98
6.00	161.25	190.95	140.97	126.29	1.14
8.00	43.51	44.31	91.58	158.13	0.48
10.0	32.19	44.75	54.13	73.34	0.59
12.0	28.33	53.61	40.94	90.07	0.69
15.0	13.40	32.29	8.74	23.21	1.53

18.0	3.36	13.89	4.59	20.98	0.73
24.0	0.00	0.00	0.00	0.00	-

Table 5. Fasting Single-Dose In Vivo Bioequivalence Study # 10016214 Arithmetic Means (±SD) of Pharmacokinetic Parameters for Nicotinuric Acid (N = 28)

PK Measures	Test (A)	Reference (B)
AUCt [ng•hr/mL]	3552.00 ± 2047.18	3576.63 ± 2104.44
AUCi [ng•hr/mL]	3896.76 ± 2308.71	4108.90 ± 2385.71
Cmax [ng/mL]	1093.22 ± 536.25	1056.02 ± 545.55
tmax [hr]	1.71 ± 0.91	1.98 ± 1.29
k_{el} [1/hr]	0.51 ± 0.22	0.50 ± 0.22
t½ [hr]	1.72 ± 1.13	1.74 ± 0.87

Table 6. Summary Statistics for Nicotinuric Acid Single-Dose In Vivo Bioequivalence Study # 10016214 Under Fasting Conditions, N = 28

PK Measures*	Geometric Mean		Within Sub Variability		Ratio of Within-Sub Variability T/R	A/B	90% CI
	Test (A)	Ref (B)	Test	Ref			
Ln AUCt (ng•hr/mL)	3152.83	3085.40	0.2164	0.1598	1.1	1.02	95.7-109.1
Ln AUCi (ng•hr/mL)	3299.70	3219.55	0.2260	0.1888	1.2	1.02	93.6-112.2
Ln Cmax (ng/mL)	1000.48	945.33	0.2094	0.2087	1.0	1.06	99.5-113.6

**geometric mean values for ln-transformed data reported*

In the case of niacin, 43 out of 126 (34%) samples showed individual ratios for AUCt between the firm's and FDA calculated values outside the range of 0.9 to 1.10. The DBE therefore reanalyzed the data using the FDA calculated AUCt values. The ratio of ln AUCt between the test and reference products and the 90% CI remained within the acceptable range.

In the case of nicotinuric acid 5 out of 126 (4.0%) samples showed individual ratios for AUCt between the firm's and FDA calculated values outside the range of 0.9 to 1.10. In the reviewer's opinion, this will not make any significant difference in the statistical outcome.

PK Reassays: None reported by the firm.

Comments on Pharmacokinetic Data:

1. The pharmacokinetic measures (AUC_t, AUC_i, C_{max}, t_{max} *and* $t_{1/2}$) and confidence intervals of AUC_t, AUC_i *and* C_{max} for niacin and nicotinuric acid as calculated by the reviewer were in agreement with the values reported by the firm.
2. In most cases, the ratios for individual AUCt between the firm's and FDA calculated values were in the range of 0.90-1.10 for both niacin and nicotinuric acid.
3. There were no statistically significant period effects for any of these PK measures.
4. The 90% confidence intervals of ln-transformed AUC_t and C_{max} ratios for niacin and nicotinuric acid are within the acceptable limits of 80-125%.
5. The 90% confidence intervals of ln-transformed AUC_i, ratio for niacin is outside the acceptable limits of 80-125%, however, that for the nicotinuric acid is within this acceptable range.
6. Results of the study showed that the parent compound could only be sporadically measured in almost one-forth of Test: replicates (15/64) and one-fifth of the reference replicates (12/64) having 8 or less quantifiable levels out of 16 samples

measured for each subject. Similarly, more than half (38/64) of the test replicates and more than one-third (23/64) of the reference replicates showed 6 or less quantifiable levels for the parent drug. Thus, no meaningful niacin AUCi profile can be expected in this study.

7. It is noted that the NDA's BA/BE studies under fasted, fed - with low fat diet, and fed -with high fat diet conditions showed that the parent compound could only be sporadically measured. Therefore, plasma nicotinuric acid was used to establish bioequivalency. Also, the PK measure AUCi has not been taken into considerations in establishing BE in the NDA studies.

   Furthermore, on May 27, 1997, in a Telecon with FDA representatives (Drs. L. Lesko, M-L Chen, J. Hunt, H-Y Ahn and M. Fossler), Dr. Tom Tozer has indicated that the innovator approach of using nicotinuric acid is reasonable in determining the bioavailability of niacin, given the complexities of niacin's non-linear saturable first-pass metabolism (page 79 of NDA review dated Jan 16, 1997). Dr. Tozer further states that *"...Niacin per se is too highly variable, etc. to do BE testing."*

   The sporadic occurrence of the parent niacin plasma data in the current submission under fasting as well as under non-fasting (see below), further supports the approach of using nicotinuric acid in determining the bioequivalence of niacin— similar to that used in the NDA.

8. The fasting study is incomplete due to deficiency in the analytical method validation on the long-term frozen stability.
9. Since the study included 13 females and 23 males, the reviewer analyzed statistical data for any gender effect. No significant difference between treatment and gender was observed for ln-AUCt, ln-AUCi and ln-Cmax data of niacin and nicotinuric acid (data not shown in the review).

Protocol No.: 10116201, The Effect of Food on the Relative Bioavailability of Two Niacin Formulations.

Study Information

Clinical Facility: ———————————————
Principal Investigator: ———————— M.D.
Clinical Study Dates: Period I: February 24, 2001, Period II: March 03, 2001
Analytical Facility: ———————————————
Chief Executive Officer: ———— (per pp. 6-1964 and 6-2041, Vol. 1.4).
Analytical Study Dates: 07/10/01 to 08/21/01
Storage Period: 179 days

Treatment ID:	A	B
Test or Reference:	T	R
Product Name:	Niacin Extended Release Tablets	Niaspan ® Tablets
Manufacturer:	Barr Laboratories, Inc.	KOS Pharmaceuticals, Inc.
Manufacturing Date:	01/18/01	N/A
Batch/Lot Number:	202141002R	0005300007
Strength:	1000 mg	1000 mg

Dosage Form:	Tablet	Tablet
Dose Administered:	1000 mg (1x1000 mg)	1000 mg (1x1000 mg)
Length of Fasting:	Overnight	Overnight
Study Condition:	Fed	Fed
Standardized Breakfast*:	Y	Y

*Standardized Breakfast consisted of the following diet:
1 Buttered English Muffin, 1 fried egg, 1 slice of American Cheese, 2 strips of bacon, 1 serving of hash brown potatoes, 240 mL of whole milk, 180 mL of orange juice.

RANDOMIZATION		**DESIGN**	
Randomized:	Y	**Design Type:**	crossover
No. of Sequences:	2	**Replicated Treatment**	N
No. of Periods:	2	**Balanced:**	N
No. of Treatments:	2	**Washout Period:**	7 days
Randomization Scheme:	**AB**: 2,3,6,8,10,11,14,16,18,19,22,24 **BA**: 1,4,5,7,9,12,13,15,17,20,21,23		

DOSING		**SUBJECTS**	
Single or Multiple Dose:	Single	**IRB Approval:**	Y
Steady State:	N	**Informed Consent Obtained:**	Y
Volume of Liquid Intake:	240 mL	**No. of Subjects Enrolled:**	24
Route of Administration:	Oral	**No. of Subjects Completing:**	23*
Dosing Interval:	N/A	**No. of Subjects Plasma Analyzed:**	23
Number of Doses:	N/A	**No. of Dropouts:**	one
Loading Dose:	N/A	**Sex(es) Included:**	Males and females**
Steady State Dose Time:	N/A	**Healthy Volunteers Only:**	Y
Length of Infusion:	N/A	**No. of Adverse Events:**	77

*Subject #9 was withdrawn from the study approximately 11 hours after Period II (Test) dosing due to adverse events - emesis.

**Demographic Data:

No of Subj	Race /Ethnic Group						Sex		Age Group (Yr.)						Height (in)		Weight (lbs.)	
Total	A[¶]	B[¶]	C[¶]	H[¶]	NA[¶]	OT[¶]	M	F	Mean*	Range[§]					Mean	Range	Mean	Range
										R1	R2	R3	R4	R5				
24	1	12	9	1	0	1	18	6	29	0	20	4	0	0	68	63-74	172	127-243

[¶] A: Asian, B: Black, C: Caucasian, H: Hispanic, NA: Native American, OT: Other (e.g., biracial)
[§] R1: <18, R2: 18-40, R3: 41-64, R4: 65-75, R5: >75

Dietary Restrictions:
Activity Restrictions:
Drug Restrictions:
Blood Sampling:

same as those reported in the fasting study*

Study Results

1) Clinical

During the study, 77 adverse events (40 Test and 37 Ref) were reported by 18 of the 24 subjects. Of the 77 adverse events, 29 were definitely related, 36 probably related, 8 possibly related, 2 remotely related and 2 unrelated to the study drugs. The most common adverse events were total body flushing, total body burning sensation, body itching and rashes. All adverse events were resolved spontaneously. These events are described in detail in Vol. 1.2, pp. 6-984 to 6-989.

Protocol Deviations: None other than minor sampling deviations.

2) **Analytical:** Same method as that used in the fasting study. Within study day assay validations are given below:

Assay Validation – Within Studv Analvte: Niacin	
Calibration Curve Standard Conc. (ng/mL)	
Inter day Precision (%CV)	
Inter day Accuracy (% Accuracy)	
r^2 value of representative calibration curve	
Linearity Range (ng/mL)	

Assay Validation – Within Study Analyte: Nicotinuric Acid	
Calibration Curve Standard Conc. (ng/mL)	
Inter day Precision (%CV)	
Inter day Accuracy (% Accuracy)	
r^2 value of representative calibration curve	
Linearity Range (ng/mL)	

Analytical Repeats:
A total of 64 out of 736 (8.7%) samples were repeated due to analytical reasons as described below:

Analytical Reasons	No of samples repeated
Values above the quantifiable limit	33
Repeated by mistake	16
Unacceptable chromatography	5
Upper limit of quantitation eliminated	9
Unacceptable internal standard	1

Comments on Analytical Methodology:

Twenty-three niacin, 4 nicotinuric acid and 6 niacin/nicotinuric acid samples were shown to have respective plasma concentrations outside the calibration range

Based on the firm's reported results, analyses for plasma niacin and nicotinuric acid for non-fasting study were completed on August 21, 2001. Considering the clinical study initiation day on February 24, 2001, the overall storage period for the plasma niacin and nicotinuric acid samples is 179 days. The firm has submitted long-term frozen stability study covering a period of 78 days only. Analytical method validation for niacin and nicotinuric acid for the assay of plasma samples obtained in the non-fasting study is therefore incomplete.

3) **Pharmacokinetic and Statistical Analysis:**
Mean Plasma Concentrations: Niacin: Table 7, Nicotinuric Acid: Table 10
Pharmacokinetics Measures: Niacin: Tables 8, 9 and13; Nicotinuric Acid: Tables 11, 12 and 14

Table 7. Non-fasting Single-Dose In Vivo Bioequivalence Study # 10116201 Arithmetic Mean Plasma Niacin Concentrations [ng/mL]* (± SD) Vs. Time (N = 23)

Time(hours)	Test Mean (A)	Test SD	Ref Mean (B)	Ref SD	A/B Ratio
0.000	0.00	0.00	0.00	0.00	-
0.500	3.42	14.89	3.44	10.47	0.99
1.00	132.15	334.12	113.37	280.26	1.17
1.50	249.53	523.41	297.84	640.79	0.84
2.00	391.99	589.90	466.05	1229.44	0.84
2.50	490.33	1156.24	423.25	813.66	1.16
3.00	472.36	537.10	681.14	1070.53	0.69
4.00	510.25	1186.78	565.41	692.81	0.90
5.00	1115.25	2043.88	1503.12	3419.46	0.74
6.00	370.42	1033.62	1000.96	2616.57	0.37
8.00	66.87	134.48	171.24	408.56	0.39
10.0	74.64	211.82	13.54	19.62	5.51
12.0	6.65	17.04	5.74	11.75	1.16
15.0	2.54	7.65	0.00	0.00	-
18.0	0.00	-	0.00	0.00	-
24.0	0.00	-	0.00	0.00	-

Table 8. Non-fasting Single-Dose In Vivo Bioequivalence Study # 10116201 Arithmetic Means (±SD) of Pharmacokinetic Parameters for Niacin, N = 23

PK Measures	Test (Non-fasting) A	Ref (Non-fasting) B
AUC_t (ng•hr/mL)	2997.13 ± 3277.53	4731.22 ± 5658.32
AUC_i (ng•hr/mL)	3451.25 ±4110.83	5134.64 ± 6276.72
C_{max} (ng/mL)	1940.95 ± 1958.67	2755.68 ± 3427.14
t_{max} (hr)	4.17 ± 1.86	4.09 ± 2.01
Kel	0.746 ± 0.60	1.04 ± 0.66
$t_{1/2}$ (hr)	1.54 ± 1.09	1.03 ± 0.73

Table 9. Summary Statistics for Niacin Single-Dose In Vivo Bioequivalence Study # 10116201 Under Non-fasting Conditions (N=23)

PK Measures*	Geometric Mean		Root Mean Square	Ratio
	Test A	Ref B		A/B
Ln AUC_t (ng•hr/mL)	2042.92	2662.74	0.7747	0.76
Ln AUC_i (ng•hr/mL)	2270.38	4039.30	0.6371	0.56
Ln C_{max} (ng/mL)	1180.82	1286.25	0.9340	0.92

**geometric mean values for ln-transformed data reported*

Table 10. Non-fasting Single-Dose In Vivo Bioequivalence Study # 10116201 Arithmetic Mean Plasma Nicotinuric Acid Concentrations [ng/mL]* (± SD) Vs. Time (N = 23)

Time(hours)	Test Mean (A)	Test SD	Ref Mean (B)	Ref SD	A/B Ratio
0.000	0.00	0.00	0.00	0.00	-
0.500	20.55	82.73	24.65	58.69	0.83
1.00	254.04	449.25	238.08	359.08	1.07
1.50	371.83	412.88	545.40	558.89	0.68
2.00	576.74	483.69	545.89	537.42	1.06
2.50	644.50	547.41	583.78	534.24	1.10
3.00	753.78	588.24	665.18	532.88	1.13
4.00	793.83	426.57	816.63	474.26	0.97
5.00	928.91	580.91	1004.91	443.52	0.92
6.00	474.35	380.08	657.57	562.61	0.72
8.00	170.82	149.08	407.34	507.95	0.42
10.0	139.74	208.86	116.60	152.00	1.20
12.0	49.95	97.27	34.01	36.54	1.47
15.0	16.87	71.18	4.96	13.50	3.40

18.0	0.91	4.36	1.12	5.36	0.81
24.0	0.00	0.00	0.00	0.00	-

Table 11. Non-fasting Single-Dose In Vivo Bioequivalence Study # 10116201Arithmetic Means (±SD) of Pharmacokinetic Parameters for Nicotinuric Acid, N = 23

PK Measures	Test (Non-fasting) A	Ref (Non-fasting) B
AUC_t (ng•hr/mL)	4656.91 ± 1795.77	5357.65 ± 1618.09
AUC_i (ng•hr/mL)	4755.00 ± 1823.72	5543.38 ± 1549.61
C_{max} (ng/mL)	1272.70 ± 505.65	1426.61 ± 473.71
t_{max} (hr)	4.24 ± 2.29	4.61 ± 1.93
Kel	0.554 ± 0.396	0.585 ± 0.202
$t_{1/2}$ (hr)	1.34 ± 0.40	1.42 ± 0.86

Table 12. Summary Statistics for Nicotinuric Acid Single-Dose In Vivo Bioequivalence Study # 10116201 Under Non-fasting Conditions (N=23)

PK Measures*	Geometric Mean		Root Mean Square	Ratio
	Test A	Ref B		A/B
Ln AUC_t (ng•hr/mL)	4349.62	5084.08	0.2209	0.86
Ln AUC_i (ng•hr/mL)	4428.84	5306.02	0.2227	0.84
Ln C_{max} (ng/mL)	1169.36	1341.71	0.3160	0.87

**geometric mean values for ln-transformed data reported*

NOTE:

The above statistical results were obtained by the reviewer based on the PK values submitted by the firm for 23 subjects completing the fed study. It was noted that the firm has used only 19 subjects for statistical calculations of the parent drug Niacin (based on information provided on pages 6-119 to 6-125, Vol. 1.1). Subjects # 2, 3, 13 and 15 have been excluded in the firm's calculation. The firm's reported statistical values on Niacin for n=19 are summarized in Table 13 below:

Table 13. Summary Statistics for Niacin Single-Dose In Vivo Bioequivalence Study # 10116201: Under Non-fasting Conditions (N=19): Firm's Reported Values*

PK Measures*	Geometric Mean		Root Mean Square	Ratio
	Test A	Ref B		A/B
Ln AUC_t (ng•hr/mL)	2453.07	2956.44	0.7976	0.83
Ln AUC_i (ng•hr/mL)	2270.59	4039.16	0.6371	0.56
Ln C_{max} (ng/mL)	1382.74	1443.26	0.9540	0.96

The reviewer recalculated the above values using the firm's provided PK data, and obtained the same statistical results.

Additionally, this reviewer also recalculated the AUCt for individual subjects based on the firm's submitted plasma Test and Reference concentrations. In most cases the ratios of the DBE's AUCt to the firm's AUCt individual subject's values were in the range of 0.94 to 1.00. However, some exceptions were noted as shown below:

Subject	Treat	AUCt Values		FDA AUCt/Firm's AUCt
		FDA calculated	Firm's Reported	
13	Test	484.8	419.0	1.16
13	Ref	432.9	357.0	1.22
14	Test	3128.9	1884.0	1.66

In addition, the reviewer's calculation did not find any significant difference in the ratios of FDA/Firm AUCt for either the Test or Reference product (0.97 and 1.00, respectively) for subject 3.

Furthermore, no plasma niacin concentration for subject #2 ref could be detected at any time point, and that for subject #15, ref could be detected only for the 8-hour time point.

The reviewer therefore, reanalyzed AUCt statistics excluding subjects 2 and 15 and using the FDA calculated values for subjects 3, 13 and 14 (i.e., a total of 21 subjects). The results are presented in the Table below.

Table 14. Summary Statistics for Niacin Single-Dose In Vivo Bioequivalence Study # 10116201: Under Non-fasting Conditions (N=21), Using Reviewer's Calculated Values for AUCt for subjects 3, 13 and 14 (Subjects 2 and 15 were excluded).

PK Measures*	Geometric Mean		Root Mean Square	Ratio
	Test A	Ref B		A/B
Ln AUC_t (ng•hr/mL)	2353.38	2807.91	0.7820	0.84
Ln AUC_i (ng•hr/mL)	2270.38	4039.30	0.6371	0.56
Ln C_{max} (ng/mL)	1299.76	1303.71	0.9162	1.00

**geometric mean values for ln-transformed data reported*

PK Repeats:

The firm has reported no PK repeat.

Comments: On pharmacokinetic/statistical data:

On the Parent Drug Niacin:

1. The pharmacokinetic measures (AUC_t, AUC_i, and C_{max}) and ratios of their ln-transformed means for niacin were recalculated by the reviewer. The reported values for AUCi and Cmax are generally in agreement with those obtained by the reviewer. There were no statistically significant period effects for any of these measures.
2. The ratios for individual AUCt between the firm's and FDA calculated values were in the range of 0.94-1.00 except in two cases subjects: #13, Test and Ref, #14, Test.
3. No plasma niacin concentration could be detected for subject #2 reference for any time point, and that for subject #15, reference could be detected only for one time point (i.e., 8-hour sampling time). Therefore, the reviewer recalculated statistical values excluding subject 2 and 15 (i.e., n = 21).
4. The ratio of geometric means for Cmax between test and reference products is within the acceptable limits of 80-125% in each case (i.e., including all subjects, n=23, excluding subjects 2, and 15, n = 21, and excluding subjects 2, 3, 13 and 15, n =19).
5. The ratio for ln-AUC_t, between test and reference products for n = 23 is outside the acceptable limit of 80-125%. However, this ratio for n = 19 (excluding subjects 2, 3, 13 and 15) as well as that for n = 21 (excluding subjects 2 and 15) was found

within the acceptable range of 80-125% as reanalyzed by the reviewer.

6. The firm's calculated ratio for ln-AUCt for n=19 (excluding subjects 2, 3, 13 and 15) is the same as that obtained by the reviewer. The firm's justification for exclusion of these subjects is as follow:

   Subjects #2, 3 and 15 (Test and Ref) and Sub #13 (Test) exhibit less than 6 measurable plasma niacin concentrations, and per protocol these data were not included in the statistical analyses (pp. 6-118, Vol. 1.1 and pp. 06-47, Vol. 1.1)".

7. Results of the study showed that the parent compound could only be sporadically measured with two-third of the subjects (Test:15/23; Ref 19/23) having 8 or less quantifiable levels out of 16 samples measured for each subject. Similarly, more than one-forth of the subjects (Test: 9/23; Ref: 6/23) showed 6 or less quantifiable levels for the parent drug. Thus, no meaningful niacin AUCi profile can be expected in this study.
8. As mentioned earlier in comment #7 on the PK study under the fasting conditions, the NDA's BA/BE studies under fasted, fed - with low fat diet, and fed -with high fat diet conditions show that the parent compound could only be sporadically measured. Therefore, plasma nicotinuric acid was used to establish bioequivalency. Furthermore, the PK measure AUCi has not been taken into considerations in establishing BE in the NDA studies.
9. In light of the above observations and the consultation with Dr. Tom Tozer (Comment #7 on the PK studies under fasting conditions), the reviewer agrees with the firm's protocol of excluding data for the subjects that exhibit less than 6 measurable plasma concentrations for statistical analyses in the case of the parent drug niacin. Additionally, in the reviewer's opinion the sporadic occurrence of the parent niacin plasma data in the current submission under non-fasting, supports the approach of using nicotinuric acid in determining the bioequivalence of niacin— similar to that used in the NDA.

On the Metabolite Nicotinuric Acid:

1. The pharmacokinetic measures (AUCt, AUCi and Cmax) and ratios of their geometric means for nicotinuric acid were recalculated by the reviewer. The reported values are in agreement with those obtained by the reviewer.
2. The ratios for individual AUCt between the firm's and FDA calculated values were in the range of 0.99-1.00 except in two cases (Sub #15: Test, 0.88 and Sub #22: Test, 0.87). In the reviewer's opinion, this will not make any significant difference in the statistical outcome.
3. The ratios for individual AUCi between the firm's and FDA calculated values were in the range of 0.95-1.00 except for one subject (Sub #24: Test, 0.91).
4. The ratio for individual Cmax between the firm's and FDA calculated values was 1 in each case.
5. The ratios of geometric means for AUC_t, AUC_i and Cmax between test non-fasting and reference non-fasting are within the acceptable limits of 0.80-1.25.

Overall Comments: On pharmacokinetic/statistical data Under Fed Conditions:
The non-fasting study is incomplete due to deficiency in the analytical method validation on long-term frozen stability.

Formulation (Not to be released under FOI)

Ingredients	Amount mg/tablet
Niacin, USP	1000
Hydroxypropyl Methylcellulose [redacted] USP	[redacted]
Povidone, USP [redacted]	[redacted]
Stearic Acid, NF	[redacted]
[redacted]	-
Total Tablet Weight	1200

* [redacted] does not appear in the final product.

Comments on Formulation:

All inactive ingredients utilized in the formulation are within the listed levels in the Inactive Ingredient Guide (1996) for oral tablets.

Dissolution

Dissolution Site: Department of Analytical Research and Development, Barr Laboratories Inc., Pomona, NY

At present there is no USP dissolution method for niacin extended-release tablets. The firm has used the following method:

Apparatus: 1 (basket), 100 rpm
Medium: Deionized water, 900 mL
Sampling Times: 1, 3, 6, 9, 12, 20 and 24 hours
Tolerance (firm's proposed): As specified below:

Time (Hours)	Amount Dissolved (%)
1	Not More Than [redacted] %
12	Not Less Than [redacted] %
24	Not Less Than [redacted] %

Number of tablets: 12

The dissolution results are summarized in the following Table:

Test Products: Niacin Extended-Release Tablet: 1000 mg
Reference Products: Niaspan® Tablet 1000 mg
Assay methodology: [redacted]

Sampling Times (Hr)	Results of In Vitro Dissolution Testing (% dissolved)					
	Test Product: Niacin Extended Release Tablets, Lot No.: 202141002R Strength: 1000 mg			Reference Product: Niaspan® Lot No.: 0005300007 Strength: 1000 mg		
	Average	Range	% RSD	Average	Range	% RSD
1	11	[redacted]	2.7	11	[redacted]	4.7
3	25		1.8	25		2.4
6	42		1.9	42		2.2
9	56		2.6	58		1.5
12	68		2.8	72		1.5
20	104		4.5	111		1.3
24	107		1.9	111		1.2

Comments on Dissolution Testing:

1. The test and reference products used in the dissolution testing were from the same lots used in the in vivo bioequivalence studies.

2. The Office of Clinical Pharmacology and Biopharmaceutics Review has recommended the following dissolution testing and specifications for the RLD (NDA 20-381, Submission date: 5/12/1997, Review date: 6/19/1997):

   Apparatus: 1 (basket), 100 rpm
   Medium: Deionized water, 900 mL
   Sampling Times: 1, 3, 6, 9, 12, 20 and 24 hours
   Tolerance: As specified below:

Time (Hours)	Amount Dissolved (%)
1	Not More Than —%
3	Between ——— %
6	Between ——— %
9	Between ———%
12	Between ———%
20	Not Less Than ——%

3. The firm's dissolution method is same as that recommended by the Agency for the RLD. However, the firm's proposed specifications are different than those recommended by the Agency. The proposed tolerance for the Test product is NLT —% (Q) in 24 hours while the Agency's recommended tolerance is NLT — % (Q) in 20 hours. In addition, the firm's specification at one-hour time-point is **Not More Than** —%, compared to the NDA's recommendation of **Not More Than** —% at this time point.

4. For extended release solid oral dosage forms, the firm is recommended to generate multipoint dissolution profiles in three additional media with different pH (e.g., pH 1.2, 4.5 and 6.8) on the test and reference products. The dissolution testing should be conducted using USP apparatus 1 (basket), 100 rpm, and 900 mL of the dissolution medium.

5. The firm should also submit similarity factor f2 values between the test and reference drug products.

6. The dissolution testing is incomplete.

Deficiencies:

1. The firm has submitted a long-term frozen stability study for niacin and nicotinuric acid covering a period of 78 days. However, the overall storage periods for the plasma niacin and nicotinuric samples in the fasting and non-fasting studies are 150 and 179 days, respectively. Thus, analytical method validations for niacin and nicotinuric acid for the assay of plasma samples under fasting and non-fasting conditions are deficient, and hence the biostudies are incomplete.

2. The firm's dissolution testing is incomplete.

Recommendations

1. The single-dose fasting and non-fasting bioequivalence studies conducted by Barr Laboratories, Inc. on its Niacin Extended Release 1000 mg Tablet, Lot #202141002R, comparing it to Niaspan® 1000 mg Tablet, Lot #0005300007 have been found incomplete by the Division of Bioequivalence due to the deficiency in the long-term frozen stability study.

2. The firm's dissolution testing is incomplete. For extended release solid oral dosage forms, the firm is recommended to generate multipoint dissolution profiles in three additional media with different pH (e.g., pH 1.2, 4.5 and 6.8) along with the similarity factor f2 between the test and reference products. The dissolution should be conducted using apparatus 1 (basket), 100 rpm, and 900 mL of the dissolution medium at sampling time 1,3,6,9,12,20 and 24 hours.

The firm should be informed of the above recommendations.

Chandra S. Chaurasia

Chandra S. Chaurasia, Ph. D.
Review Branch I
Division of Bioequivalence

Date: 4/22/2002

APPEARS THIS WAY
ON ORIGINAL

RD INITIALED YHUANG
FT INITIALED YHUANG Date: 5/1/2002

Concur: Date: 5/2/02
Dale P. Conner, Pharm.D.
Director, Division of Bioequivalence

ANDA: 76-250 APPLICANT: Barr Laboratories, Inc.
DRUG PRODUCT: Niacin Extended Release Tablets, 1000 mg
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CC: DIVISION FILE, HFD-652/Bio Secretary-Bio Drug File, HFD-650/C.Chaurasia

BIOEQUIVALENCY COMMENTS TO BE PROVIDED TO THE APPLICANTS

ANDA: 76-250 APPLICANT: Barr Laboratories, Inc.

DRUG PRODUCT: Niacin Extended Release Tablets, 1000 mg

The Division of Bioequivalence has completed its review of your submission acknowledged on the cover sheet. The following deficiencies have been identified:

You have submitted a long-term frozen stability study covering a period of 78 days only. However, the overall storage periods for the plasma niacin and nicotinuric acid samples are 150 and 179 days, respectively for the fasting and non-fasting studies. Therefore, analytical method validations for niacin and nicotinuric acid are deficient, and the biostudies under fasting and non-fasting conditions are incomplete.

The in vitro dissolution testing conducted on your niacin extended release tablets, 1000 mg is incomplete. The Division recommends that you conduct additional dissolution testing using the following conditions:

Apparatus: USP Apparatus 1 (basket), 100 rpm
Medium: Buffer pH 1.2, 4.5 and 6.8, 900 mL
No. of Sampling Units: 12
Sampling Time: 1,3,6,9,12,20 and 24 hours.

Please also submit similarity factor f2 between the test and reference products.

Sincerely yours,

Dale P. Conner, Pharm.D.
Director, Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

CC: ANDA 76-250
ANDA DUPLICATE
DIVISION FILE
HFD-652/Bio Secretary-Bio Drug File
HFD-650/C.Chaurasia

Endorsements: (Draft and Final with Dates)
HFD-652/CS Chaurasia 4/22/2002
HFD-652/YC Huang 5/1/2002
HFD-617/K Scardina 5/3/02
HFD-650/Dale Conner 5/2/02

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Printed in Final on 04/22/2002

BIOEQUIVALENCY – **Incomplete** Submission Dates: 10/02/2001
Dissolution - **Incomplete**

1. **FASTING STUDY** (STF) oic Strength: **1000 mg**
_____ (Clinical)
_____ (Analytical) Outcome: **IC**

2. **FOOD STUDY** (STP) oic Strength: **1000 mg**
_____ (Clinical)
_____ (Analytical) Outcome: **IC**

~~**DISSOLUTION TESTING**~~ KS 5/7/02 Strengths: **1000 mg**
Outcome: **IC**

Outcome Decisions: **IC** - Incomplete

WinBio Comments:

- Fasting and non-fasting bioequivalence studies on Niacin Extended Release Tablets, 1000 mg are incomplete.
- Dissolution testing on Niacin Extended Release Tablets, 1000 mg is incomplete.

Niacin Extended Release Tablets
1000 mg
ANDA 76-250
Reviewer: Chandra S. Chaurasia

Barr Laboratories, Inc.
Pomona, NY 10970
Submission Date:
05/17/2002

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Review of an Amendment

Introduction

First Generic: Yes

Contents of Submission:

1. Analytical Method Validation, and
2. Dissolution data.

Reference Listed Drug: Niaspan® (Niacin, NDA 20381, July 28, 1997) tablets are available as 375 mg, 500 mg, 750 mg and 1000 mg extended release tablets manufactured by KOS Pharmaceutical. The Orange Book (Electronic 2002) lists each of these Niaspan® extended release tablets as the reference listed drugs. In addition, the Orange Book also lists NIASPAN TITRATION STARTER PACK containing Niacin 375 mg, 500 mg and 750 mg extended-release tablets under the same NDA 20831.

Barr Laboratories previously submitted single-dose bioequivalence studies under fasting and non-fasting conditions comparing its Niacin Extended Release 1000 mg Tablet, Lot #202141002R to Niaspan® 1000 mg Tablet, Lot #0005300007, manufactured by KOS Pharmaceutical (Submission Date: October 02, 2001; Review Date: May 02, 2002). The biostudies were found incomplete due to the deficiency in the long-term frozen stability study for niacin and nicotinuric acid. In the original application, the firm has submitted a long-term frozen stability study covering a period of 78 days only. Whereas, the overall storage period for the plasma Niacin and Nicotinuric acid samples in the fasting and non-fasting study were 150 and 179 days, respectively.

In addition, the dissolution testing method used by the firm in the original application was incomplete. The firm was recommended to generate multipoint dissolution profiles in three additional media with different pH (e.g., pH 1.2, 4.5 and 6.8) along with the similarity factor f2 between the test and reference products using the following conditions:

Apparatus: USP Apparatus 1 (basket), 100 rpm
Medium: Buffer pH 1.2, 4.5 and 6.8, 900 mL
No. of Sampling Units: 12
Sampling Time: 1,3,6,9,12,20 and 24 hours.

In the current submission, the firm has responded to the above deficiencies.

REVIEW OF THE FIRM'S RESPONSE

Deficiency 1: *You have submitted a long-term frozen stability study covering a period of 78 days only. However, the overall storage periods for the plasma niacin and nicotinuric acid samples are 150 and 179 days, respectively for the fasting and non-fasting studies. Therefore, analytical method validations for niacin and nicotinuric acid are deficient, and the biostudies under fasting and non-fasting conditions are incomplete.*

Firm's Response:

The firm has provided additional long-term frozen stability data for niacin and nicotinuric acid in plasma stored at –20 °C for 183 days. Six sets of controls at concentrations of low QC (50.0 ng/mL), medium QC (250 ng/mL) and high QC (1400 ng/mL) were stored at –20 °C , and analyzed after 183 days using a standard curve prepared from a fresh stock solution. The results show that the percent changes for niacin/nicotinuric acid in human plasma over the storage period of 183 days were 7.2%/11.8%, 8.4%/10.4% and 3.8%/4.5%, for the 50.0, 250 and 2500 ng/mL concentrations, respectively.

Comments on Analytical Methodology:

The analytical method validations for niacin and nicotinuric acid are acceptable.

Deficiency 2: *The in vitro dissolution testing conducted on your niacin extended release tablets, 1000 mg is incomplete. The Division recommends that you conduct additional dissolution testing using the following conditions*:

Apparatus: USP Apparatus 1 (basket), 100 rpm
Medium: Buffer pH 1.2, 4.5 and 6.8, 900 mL
No. of Sampling Units: 12
Sampling Time: 1,3,6,9,12,20 and 24 hours.

Please also submit similarity factor f2 between the test and reference products.

Firm's Response:

The firm has provided comparative dissolution testing profile on niacin tablets 1000 mg in three additional pH using the Agency's recommended method described above.

Dissolution Site: Barr Laboratories Inc., Pomona, NY

The dissolution results are summarized in Tables 1-3 below. For comparison, dissolution results obtained using deionized water as the dissolution medium are also provided in Table 4.

Table 1. Dissolution Results: Medium: USP pH 1.2

Test Products: Niacin Extended-Release Tablet: 1000 mg
Reference Products: Niaspan® Tablet 1000 mg

Assay methodology: ——

Results of In Vitro Dissolution Testing (% dissolved)

Sampling Times (Hr)	**Test Product: Niacin Extended Release Tablets, Lot No.: 202141002R Strength: 1000 mg**			**Reference Product: Niaspan® Lot No.: 0005300007 Strength: 1000 mg**		
	Average	Range	% RSD	Average	Range	% RSD
1	20		2.6	21		2.5
3	39		2.4	40		1.7
6	59		2.2	60		1.1
9	74		2.3	78		1.2
12	87		2.4	90		1.0
20	103		1.5	103		0.8
24	103		1.4	104		0.8
F2= 83						

Table 2. Dissolution Results: Medium: USP pH 4.5 Buffer

Test Products: Niacin Extended-Release Tablet: 1000 mg
Reference Products: Niaspan® Tablet 1000 mg

Assay methodology: ——

Results of In Vitro Dissolution Testing (% dissolved)

Sampling Times (Hr)	**Test Product: Niacin Extended Release Tablets, Lot No.: 202141002R Strength: 1000 mg**			**Reference Product: Niaspan® Lot No.: 0005300007 Strength: 1000 mg**		
	Average	Range	% RSD	Average	Range	% RSD
1	12		3.2	11		0.0
3	25		3.6	24		1.6
6	41		3.4	40		1.7
9	54		3.5	54		1.7
12	65		3.3	66		1.7
20	98		7.5	103		0.7
24	102		0.9	104		0.8
F2= 81						

Table 3. Dissolution Results: Medium: USP pH 6.8 Buffer

Test Products: Niacin Extended-Release Tablet: 1000 mg
Reference Products: Niaspan® Tablet 1000 mg

Assay methodology: ——

Results of In Vitro Dissolution Testing (% dissolved)

Sampling Times (Hr)	**Test Product: Niacin Extended Release Tablets, Lot No.: 202141002R Strength: 1000 mg**			**Reference Product: Niaspan® Lot No.: 0005300007 Strength: 1000 mg**		
	Average	Range	% RSD	Average	Range	% RSD
1	12		4.1	13		3.8
3	25		2.6	26		2.0
6	38		2.6	40		1.3
9	48		2.4	52		1.0
12	57		2.4	62		0.7
20	81		9.9	88		5.6
24	95		8.8	104		0.5
F2= 65						

Table 4. Dissolution Results: Medium: Deionized Water (submitted in the original applications)

Test Products: Niacin Extended-Release Tablet: 1000 mg Reference Products: Niaspan® Tablet 1000 mg Apparatus 1 (basket), 100 rpm, 900 mL, **Deionized Water**						
Assay methodology:						
Results of In Vitro Dissolution Testing (% dissolved)						
Sampling Times (Hr)	**Test Product: Niacin Extended Release Tablets, Lot No.: 202141002R Strength: 1000 mg**			**Reference Product: Niaspan® Lot No.: 0005300007 Strength: 1000 mg**		
	Average	Range	% RSD	Average	Range	% RSD
1	11		2.7	11		4.7
3	25		1.8	25		2.4
6	42		1.9	42		2.2
9	56		2.6	58		1.5
12	68		2.8	72		1.5
20	104		4.5	111		1.3
24	107		1.9	111		1.2
F2= 72						

Comments on Dissolution Testing:

1. The test and reference products used in the dissolution testing were from the same lots used in the in vivo bioequivalence studies.

2. At present there is no USP dissolution method for niacin extended-release tablets. The FDA has recommended the following method for the RLD (NDA 20-381, Submission date: 5/12/1997, Review date: 6/19/197):

   Apparatus: 1 (basket), 100 rpm
   Medium: Deionized water, 900 mL
   Sampling Times: 1, 3, 6, 9, 12, 20 and 24 hours
   Tolerance: As specified below:

Time (Hours)	Amount Dissolved (%)
1	Not More Than —%
3	Between ——— %
6	Between ——— %
9	Between ——— %
12	Between ——— %
20	Not Less Than ___ %

3. The dissolution results in pH 4.5 and 6.8 are similar to those originally reported by the firm using water as the medium. The similarity factor f2 between the test and reference products in each case is more than 50.
4. At 1, 3, 6, 9 and 12-hr time points, both the test and reference products exhibit significantly higher dissolution in pH 1.2 than that at the corresponding time points in water, pH 4.5 and pH 6.8.

5. It is further noted that labeling indicates *"to maximize bioavailability and reduce the risk of gastrointestinal (GI) upset, Niaspan should be taken at bedtime after a low-fat snack"*. Thus, in principle, the pH should be reasonably higher than 1.2 at the time of drug administration, and dose dumping may not be an issue.
6. Firm's dissolution is acceptable.
7. Based on the reported dissolution testing results in different media, the firm's dissolution method in water using apparatus I (basket), 100 rpm should be recommended for the manufacturing controls and stability programs.

Recommendations

1. The single-dose fasting and non-fasting bioequivalence studies conducted by Barr Laboratories, Inc. on its Niacin Extended Release 1000 mg Tablet, Lot #202141002R, comparing it to Niaspan® 1000 mg Tablet, Lot #0005300007 have been found acceptable by the Division of Bioequivalence. The studies demonstrate that Barr's Niacin Extended Release 1000 mg tablets are bioequivalent to the reference drug Niaspan 1000 mg tablets manufactured by KOS Pharmaceuticals.
2. The firm has conducted an acceptable dissolution testing on its Niacin Extended Release 1000-mg tablets, Lot #202141002R.
3. The dissolution testing should be incorporated into the firm's manufacturing controls and stability programs. The dissolution testing should be conducted in 900 mL of deionized water at 37 ^{0}C using USP apparatus I (basket) at 100 rpm. The test products should meet the following interim specifications:

Time (Hours)	Amount Dissolved (%)
1	**Not More Than —%**
3	Between ——— %
6	Between ——— %
9	Between ——— %
12	Between ——— %
20	**Not Less Than — %**

These values were revised. See bioreview dated 1/28/03. /Chandra 5/8/03

4. From bioequivalence point of view, the firm has met the requirements for *in vivo* bioequivalence and *in vitro* dissolution testing and the application is approvable.

The firm should be informed of the above recommendations.

Chandra S. Chaurasia

Chandra S. Chaurasia, Ph. D.
Review Branch I
Division of Bioequivalence

Date: 6/19/2002

RD INITIALED YHUANG
FT INITIALED YHUANG Date: 6/19/2002

Concur: Date: 8/1/02
Dale P. Conner, Pharm.D.
Director, Division of Bioequivalence

ANDA: 76-250 APPLICANT: Barr Laboratories, Inc.
DRUG PRODUCT: Niacin Extended Release Tablets, 1000 mg
V:\firmsnz\Barr\ltrs&rev\76250A502.doc
CC: DIVISION FILE, HFD-652/Bio Secretary-Bio Drug File, HFD-650/C.Chaurasia

APPEARS THIS WAY
ON ORIGINAL

BIOEQUIVALENCY COMMENTS TO BE PROVIDED TO THE APPLICANTS

ANDA: 76-250 APPLICANT: Barr Laboratories, Inc.

DRUG PRODUCT: Niacin Extended Release Tablets, 1000 mg

The Division of Bioequivalence has completed its review of your submission acknowledged on the cover sheet, and has no further questions at this time.

We acknowledge that the following dissolution testing has been incorporated into your manufacturing controls and stability program:

The dissolution testing should be conducted in 900 mL of water at 37 ºC using USP apparatus I (basket) at 100 rpm. The test products should meet the following interim specifications:

Time (Hours)	Amount Dissolved (%)
1	**Not More Than —%**
3	Between ——— %
6	Between ——— %
9	Between ——— %
12	Between ——— %
20	**Not Less Than ——%**

Please note that the bioequivalency comments provided in this communication are preliminary. These comments are subject to revision after review of the entire application, upon consideration of the chemistry, manufacturing and controls, microbiology, labeling, or other scientific or regulatory issues. Please be advised that these regulatory reviews may result in the need for additional bioequivalency information and/or studies, or may result in a conclusion that the proposed formulation is not approvable.

Sincerely yours,

Dale P. Conner

Dale P. Conner, Pharm.D.
Director, Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

CC: ANDA 76-250
ANDA DUPLICATE
DIVISION FILE
HFD-652/Bio Secretary-Bio Drug File
HFD-650/C.Chaurasia

Endorsements: (Draft and Final with Dates) 6/19/2002
HFD-652/CS Chaurasia
HFD-652/YC Huang 6/19/2002
HFD-617/K Scardina 6/5/02
HFD-650/Dale Conner 8/1/02

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Printed in Final on 06/19/2002

BIOEQUIVALENCY – **Acceptable**
Dissolution - **Acceptable**

Submission Dates: 05/17/2002

STUDY Amendment (STA) 01C

Strength**: 1000 mg**
Outcome**: AC**

Outcome Decisions: **AC** - Acceptable

WinBio Comments:

- Fasting and non-fasting bioequivalence studies on Niacin Extended Release Tablets, 1000 mg are acceptable.
- Dissolution testing on Niacin Extended Release Tablets, 1000 mg is acceptable.

OFFICE OF GENERIC DRUGS
DIVISION OF BIOEQUIVALENCE

5

ANDA #: 76-250 SPONSOR: Barr Laboratories, Inc.

DRUG AND DOSAGE FORM: **Niacin Extended Release Tablets**

STRENGTH (S): **1000 mg**

TYPES OF STUDIES: Fasting and non-fasting Bioequivalence Studies on 1000-mg strength.

CLINICAL STUDY SITE (S): _____

ANALYTICAL SITE (S): _____

STUDY SUMMARY : Bioequivalence studies are acceptable

DISSOLUTION: Dissolution testing is acceptable

DSI INSPECTION STATUS

Inspection needed: NO	Inspection status:	Inspection results:
First Generic No New facility _____ For cause _____ Other _____	Inspection requested: (date) Inspection completed: (date)	

PRIMARY REVIEWER : CHANDRA S. CHAURASIA, Ph. D. BRANCH : I

INITIAL : CS Chaurasia DATE : 6/19/2002

TEAM LEADER : YIH-CHAIN HUANG, Ph. D. BRANCH : I

INITIAL : YCH DATE : 6/19/2002

DIRECTOR, DIVISION OF BIOEQUIVALENCE : DALE P. CONNER, Pharm. D.

INITIAL : DPC DATE : 8/1/02

JAN 28 2003

DIVISION OF BIOEQUIVALENCE REVIEW

ANDA No.	76-250 & 76-378
Drug Product Name	Niacin ER Tablets
Strength	1000 mg, 750 mg & 500 mg
Applicant Name	Barr Laboratories
Address	Pomona, NY
Amendment Submission Date(s)	December 13, 2002
Reviewer	Hoainhon Nguyen
File Location	v:\firmsam\barr\ltrs&rev\76250a1202.doc

I. Executive Summary

The firm has submitted the current amendments to acknowledge the Agency's recommended dissolution method as specified in the August 12, 2002 letter to the firm. In addition, the firm is proposing specifications that differ from what the Agency is recommending for the time points 3, 6, 9 and 12 hours.

	Agency's Recommended Specifications	Barr's Proposed Specifications
1 hour	NMT —%	NMT — %
3 hours	—— %	—— %
6 hours	—— %	—— %
9 hours	—— %	—— %
12 hours	—— %	—— %
20 hours	NLT —%	NLT — %

The DBE found the proposed dissolution specifications are in accordance with the Guidance for Industry: Extended Release Oral Dosage Forms: Development, Evaluation, and Application of In Vitro/In Vivo Correlation. Therefore, the proposed specifications are acceptable. The firm is recommended to incorporate the *interim* specifications into its control and stability dissolution testing program. The firm may submit dissolution data for three production lots, to finalize the *interim* specifications or to determine if further revision of the *interim* dissolution specification is warranted.

II. Table of Contents

III. Submission Summary

A. Drug Product Information

Test Product Barr's Niacin ER Tablets
Reference Product Niaspan ER Tablets (NDA #20-381, KOS Pharmaceuticals, Approved 07/28/97)
Indication Lipid-lowering agent indicated as an adjunct to diet when the response to a diet restricted in saturated fat and cholesterol has been inadequate.

PK/PD Information Not applicable to the subject of the amendment.

B. Contents of Submission

	How many?
Amendments X	2 amendments (1 for ANDA #76-250, 1 for ANDA # 76-378)

C. Bioanalytical Method Validation (Pre-Study, Vol. Pages.) N/A

D. In Vivo Studies N/A

E. Formulation N/A

F. In Vitro Dissolution

Recommended Method:

Medium	water
Volume (mL)	900 mL
USP Apparatus Type	I (basket)
Rotation (rpm)	100 rpm

Firm's proposed and FDA-recommended specifications:

	Agency's Recommended Specifications	Barr's Proposed Specifications
1 hour	NMT —%	NMT —%
3 hours	—— %	—— %
6 hours	—— %	—— %
9 hours	—— %	—— %
12 hours	—— %	—— %
20 hours	NLT —%	NLT —%

See the dissolution data submitted and summarized in the following reviews: v:\firmsam\barr\ltrs&rev\76250o502.doc and v:\firmsam\barr\ltrs&rev\76378nd302.doc

G. **Waiver Request** N/A

H. Comments

1. As the firm pointed out, according to the Guidance for Industry for Extended Release Oral Dosage Forms: Development, Evaluation, and Application of In Vitro/In Vivo Correlation, *"The recommended range at any dissolution time point specification is ±10% deviation from the mean dissolution profile obtained from the clinical/bioavailability lots. In certain cases, reasonable deviations from ±10% range can be accepted provided that the range at any time point does not exceed 25%."* Following are the mean initial dissolution profiles of the bio lots of 1000 mg, 750 mg and 500 mg strengths.

Time	1000 mg	750 mg	500 mg
1 hour	11%	12%	12%
3 hours	25%	24%	26%
6 hours	42%	38%	42%
9 hours	56%	50%	55%
12 hours	68%	61%	66%
20 hours	104%	85%	90%

The proposed specifications reflect the ranges of ±10% deviation from the similar mean dissolution profiles of the 1000 mg and 500 mg, and also bracket the mean dissolution profile of the 750 mg strength, which has a slightly different profile from the other two strengths. Therefore, the proposed specifications are in agreement with the Guidance for Industry for Extended Release Oral Dosage Forms.

2. It should be noted that the original specifications recommended by the FDA for the test product were based on the specifications recommended for NDA 20-381 (Niaspan ER Tablets), in the NDA submission dated 05/12/97, and not based on the actual dissolution data from the test product's bio lots (See the review v:\firmsam\barr\ltrs&rev\76250o502.doc).

3. It should also be noted that in the current amendments, the firm also submitted the stability data for the bio lots of the 3 strengths. However, the stability data were not taken into consideration by the DBE for evaluating the proposed specifications. In addition, the stability data showed a slight downward trend during the 21-month stability testing period (within the recommended specifications), but the firm actually proposed increased dissolution limits at time points 3, 6, 9 and 12 hours.

4. Based on the information provided and discussed above, the proposed dissolution specifications are found acceptable.

I. Recommendations

The DBE found the proposed dissolution specifications are in accordance with the Guidance for Industry: Extended Release Oral Dosage Forms: Development, Evaluation, and Application of In Vitro/In Vivo Correlation. Therefore, the proposed specifications are acceptable. The firm is recommended to incorporate the following dissolution testing and *interim* specifications into its control and stability dissolution testing program. The firm may submit dissolution data for three production lots, to finalize the *interim* specifications or to determine if further revision of the *interim* dissolution specification is warranted.

The dissolution testing should be conducted in 900 mL of deionized water at 37 ^{0}C using USP apparatus I (basket) at 100 rpm. The test products should meet the following interim specifications:

Time (Hours)	Amount Dissolved (%)
1	Not More Than —%
3	Between ——— %
6	Between ——— %
9	Between ——— %
12	Between ——— %
20	Not Less Than —%

Hoainhon Nguyen, Review Branch

Yih Chain Huang 1/24/2003
Team Leader, Review Branch I

Dale P. Conner 1/28/03
Dale P. Conner, Pharm. D.
Director, Division of Bioequivalence
Office of Generic Drugs

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BIOEQUIVALENCY COMMENTS TO BE PROVIDED TO THE APPLICANTS

ANDA: 76-250 & 76-378 APPLICANT: Barr Laboratories, Inc.

DRUG PRODUCT: Niacin Extended Release Tablets, 1000 mg, 750 mg & 500 mg

The Division of Bioequivalence has completed its review of your submission acknowledged on the cover sheet, and has no further questions at this time.

The proposed dissolution specifications have been found acceptable as they are in accordance with the Guidance for Industry: Extended Release Oral Dosage Forms: Development, Evaluation, and Application of In Vitro/In Vivo Correlation.

We acknowledge that the following dissolution testing and the proposed *interim* specifications have been incorporated into your manufacturing controls and stability program. You may submit dissolution data for three production lots, to finalize the *interim* specifications or to determine if further revision of the *interim* dissolution specifications is warranted.

The dissolution testing should be conducted in 900 mL of deionized water at 37 ^{0}C using USP apparatus I (basket) at 100 rpm. The test products should meet the following interim specifications:

Time (Hours)	Amount Dissolved (%)
1	Not More Than —%
3	Between ————%
6	Between ————%
9	Between ————%
12	Between ————%
20	Not Less Than ——%

Please note that the bioequivalency comments provided in this communication are preliminary. These comments are subject to revision after review of the entire application, upon consideration of the chemistry, manufacturing and controls, microbiology, labeling, or other scientific or regulatory

issues. Please be advised that these regulatory reviews may result in the need for additional bioequivalency information and/or studies, or may result in a conclusion that the proposed formulation is not approvable.

Sincerely yours,

Dale P. Conner, Pharm.D.
Director, Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

APPEARS THIS WAY
ON ORIGINAL

CC: ANDA 76-250 & 76-378
ANDA DUPLICATE
DIVISION FILE
HFD-652/Bio Secretary-Bio Drug File
HFD-650/HNguyen

Endorsements: (Draft and Final with Dates)
HFD-652/HNguyen
HFD-652/YC Huang YH 1/24/2003
HFD-617/A. Sigler
HFD-650/Dale Conner DK 1/28/03

V:\firmsnz\Barr\ltrs&rev\76250A1202.doc

Printed in Final on

BIOEQUIVALENCY – **Acceptable**
DISSOLUTION - **Acceptable**

Submission Dates: 12/13/2002

1. **Study Amendment** (STA) OK only STA YH

   Strength: **1000 mg**
   Outcome: **AC**

2. **Study Amendment** (STA) OK

   Strength: **750 mg & 500 mg**
   Outcome: **AC**

Outcome Decisions: **AC** - Acceptable

WinBio Comments:

APPEARS THIS WAY
ON ORIGINAL

OFFICE OF GENERIC DRUGS
DIVISION OF BIOEQUIVALENCE

ANDA # : 76-250 & 76-378 SPONSOR : Barr Laboratories
DRUG AND DOSAGE FORM : Niacin ER Tablets
STRENGTH(S) : 1000 mg, 750 mg & 500 mg
TYPES OF STUDIES : N/A
CINICAL STUDY SITE(S) : N/A
ANALYTICAL SITE(S) : N/A

STUDY SUMMARY : N/A
DISSOLUTION : Proposed dissolution specifications are acceptable
WAIVER REQUEST: N/A

DSI INSPECTION STATUS

Inspection needed: NO	Inspection status:	Inspection results:
First Generic YES	Inspection requested: (date)	
New facility _____	Inspection completed: (date)	
For cause _____		
Other _____		

PRIMARY REVIEWER : Hoainhon Nguyen BRANCH : I
INITIAL : HNe DATE : 1/24/03

TEAM LEADER : Yih-Chain Huang BRANCH : I
INITIAL : YCH DATE : 1/24/2003

DIRECTOR, DIVISION OF BIOEQUIVALENCE : DALE P. CONNER, Pharm. D.

INITIAL : DPC DATE : 1/28/03

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 76-250

ADMINISTRATIVE DOCUMENTS

M E M O R A N D U M

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE : October 23, 2001

TO : Director
Division of Bioequivalence (HFD-650)

FROM : Chief, Regulatory Support Branch
Office of Generic Drugs (HFD-615) 23-OCT-2001

SUBJECT: Examination of the bioequivalence study submitted with an ANDA for Niacin Extended-release Tablets, 1000 mg (1 GM) to determine if the application is substantially complete for filing and/or granting exclusivity pursuant to U.S.C. 355 (j)(5)(B)(iv).

Bar Laboratories, Inc. has submitted AND 76-250 for Niacin Extended-release Tablets, 1000 mg (1 GM). The ANDA contains a certification pursuant to 21 U.S.C. 355 (j)(2)(A)(vii)(iv) stating that patent(s) for the reference listed drug will not be infringed by the manufacturing or sale of the proposed product. Also it is a first generic. In order to accept an AND that contains a first generic, the Agency must formally review and make a determination that the application is substantially complete. Included in this review is a determination that the bioequivalence study is complete, and could establish that the product is bioequivalent.

Please evaluate whether the study submitted by Bar on October 2, 2001 for its Niacin product satisfies the statutory requirements of "completeness" so that the AND may be filed.

A "complete" bioavailability or bioequivalence study is defined as one that conforms with an appropriate FDA guidance or is reasonable in design and purports to demonstrate that the proposed drug is bioequivalent to the "listed drug".

AND 76-250

In determining whether a bio study is "complete" to satisfy statutory requirements, the following items are examined:

1. Study design

   (a) Appropriate number of subjects
   (b) Description of methodology

2. Study results

   (a) Individual and mean data is provided
   (b) Individual demographic data
   © Clinical summary

The issue raised in the current situation revolves around whether the study can purport to demonstrate bioequivalence to the listed drug.

We would appreciate a cursory review and your answers to the above questions as soon as possible so we may take action on this application.

DIVISION OF BIOEQUIVALENCE:

✓ Study meets statutory requirements 11/1/2001

_____ Study does **NOT** meet statutory requirements

Reason:

Director, Division of Bioequivalence

11/2/01
Date

BIOEQUIVALENCE CHECKLIST FOR APPLICATION COMPLETENESS

ANDA 76-250 DRUG NAME NIACIN ER 1000 MG FIRM BARR LABS.

DOSAGE FORM(s) TABLET

	YES	NO	REQUIRED AMOUNT	AMOUNT SENT	COMMENTS
Protocol	✓				Fasting study & Food study.
Assay Methodology	✓				
Procedure SOP	✓				
Methods Validation	✓				
Study Results Ln/Lin	✓				
Adverse Events	✓				
IRB Approval	✓				
Dissolution Data	✓				
Pre-screening of patients	✓				
Chromatograms	✓				
Consent forms	✓				
Composition	✓				
Summary of study	✓				
Individual Data & Graphs , Linear & Ln	✓				
PK/PD data disk	✓				
Randomization Schedule	✓				
Protocol Deviations	✓				

	YES	NO	REQUIRED AMOUNT	AMOUNT SENT	COMMENTS
Clinical site	✓				
Analytical site	✓				
Study investigators	✓				
Medical Records	✓				
Clinical Raw Data	✓				
Test Article Inventory	✓				
BIO Batch Size	✓				
Assay of active content drug	✓				
Content uniformity	✓				
Date of manufacture	✓				1/18/2001, Fast & Fed studies started 2/24/01
Exp. Date RLD	✓				
Biostudy lot numbers	✓				
Statistics	✓				Used average bioequivalence approach in data analysis
Summary results provided by the firm indicate studies pass BE criteria	✓				See Attachment 1
Waiver requests for other strengths / supporting data		✓			NA - Only one strength submission

Additional comments:

Recommendation: (COMPLETE) / INCOMPLETE YH 11/1/2001

Reviewed by

James E. Chaney Date 10/31/2001

Revised 6/7/2000

RECORD OF TELEPHONE CONVERSATION

Reference is made to minor amendment dated December 13, 2002. **76-250:** **FDA**: Please submit your 24 month stability data using the most recent specifications. Also, please include data at each time point. **Firm**: Mr. Ahmed informed us that the full term stability data will be available February 14, 2003. **76-378:** **FDA**: We recognize that there may have been a typo error when you claimed to have —month stability data in your December 13, 2002 submission. Since your data only reflects 12 months of stability data, we recommend that you either reduce the expiry dating to 12 months or provide up to date stability data (15 months). Also, please continue to perform stability testing, and submit the information accordingly. **Firm**: Mr. Ahmed stated that Barr Laboratories did not save the accelerated samples, and they should have 15 months of data by February 14, 2003. Also, Mr. Ahmed made a commitment to revise the request for 24 month expiry dating, as well as correct the typo form the December 13, 2002 submission. I indicated to Mr. Ahmed that I would forward the Bioequivalency comments for his review. Fax date: 2/5/03 Fax time: 12:45PM	**DATE:** February 5, 2003 **ANDA NUMBER:** 76-250 & 76378 **PRODUCT NAME:** Niacin Extended Release Tablets **INITIATED BY:** **Firm** __ **Agency_X_** **FIRM NAME:** Barr Laboratories Inc. **FIRM REPRESENTATIVE:** Sharif Ahmed **TELEPHONE NUMBER:** 845-348-8051 **FDA REPRESENTATIVE:** Shing Liu Bing Cai Wanda Pamphile **SIGNATURE** Shing Liu Bing Cai Wanda Pamphile

Orig: ANDA 76-250 & 76378
Cc: Division File
Chem. I telecon binder

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OGD APPROVAL ROUTING SUMMARY

ANDA #76-250 **Applicant** Barr Laboratories, Inc.
Drug Niacin Extended-release Tablets **Strength** 1000 mg

)PROVAL ☐ **TENTATIVE APPROVAL** ☒ **SUPPLEMENTAL APPROVAL (NEW STRENGTH)** ☐ **OTHER** ☐

REVIEWER:
1. Project Manager, Wanda Pamphile
Review Support Br Team 5

DRAFT Package
Date 4/20/03
Initials WP

FINAL Package
Date _____
Initials _____

Application Summary:
Original Rec'd date 10/2/01
Date Acceptable for Filing 10/3/01
Patent Certification (type) IV 10/3/01
Date Patent/Exclus.expires 9/20/13; 5/27/17
Citizens' Petition/Legal Case Yes ☐ No ☒
(If YES, attach email from PM to CP coord)
First Generic Yes ☒ No ☐
(If YES, Pediatric Exclusivity Tracking System (PETS)

EER Status Pending ☐ Acceptable ☒ OAI ☐
Date of EER Status 10/17/02
Date of Office Bio Review 3/31/03
Date of Labeling Approv. Sum 4/29/02
Date of Sterility Assur. App. N/A
Methods Val. Samples Pending Yes ☒ No ☐
Commitment Rcd. from Firm Yes ☒ No ☐
Modified-release dosage form: Yes ☒ No ☐

RLD = **Niaspan®**
Date checked 4/22/03 NDA# 20-381
Nothing Submitted ☒
Written request issued ☐
Study Submitted ☐

Interim Dissol. Specs in (AP) Ltr: Yes ☐ No
TA ltr.

Previously reviewed and tentatively approved ☐ Date _____
Previously reviewed and CGMP def./N/A Minor issued ☐ Date _____
Comments:

Gregg Davis **PPIV ANDAs Only**
Supv., Reg. Support Branch/

Date 4/23/03
Initials [illegible] acting

Date 4/23/03
Initials [illegible] acting

Contains GDEA certification: Yes ☑ No ☐
(required if sub after 6/1/92)
Patent/Exclusivity Certification: Yes ☑ No ☐
If Para. IV Certification- did applicant
Notify patent holder/NDA holder Yes ☑ No ☐
Was applicant sued w/in 45 days: Yes ☑ No ☐
Has case been settled: Yes ☐ No ☑
Date settled:
Is applicant eligible for 180 day
Generic Drugs Exclusivity for each strength: (1000mg) Yes ☑ No ☐

Determ. of Involvement? Yes ☐ No ☐

Pediatric Exclusivity System
Date Checked 4/23/03
Nothing Submitted ☑
Written request issued ☐
Study Submitted ☐

RLD = Niaspan Extended-release Tablets
Kos Pharmaceuticals, Inc. is currently the only approved product
Barr is currently the only applicant in house
NDA 20-381 (004)

Comments: ~~Ok~~ Patents 6080428 & 6129930 → 30 month exp. 7/23/04
Patent 6,436,715 → 30 month exp. 3/30/05

(Sorry about the handwriting, it's tough to write TA CAST)

3. Div. Dir./Deputy Dir.
Chemistry Div. I or II
Comments:

Date 5/5/03
Initials [illegible]

no impairment at 24 months dissolution OK

REVIEWER: **FINAL ACTION**

4. Frank Holcombe
Assoc. Dir. For Chemistry
Comments: (First generic drug review) Satisfactory

Date 5-1-03
Initials JSH

5. Peter Rickman
Director, DLPS

Date 5/8/03
Initials for

Para.IV Patent Cert: Yes☐ No☐; Pending Legal Action: Yes☐ No☐; Petition: Yes☐ No☐
Comments: Acceptable EES dated 10/1/02 (Verified 5/8/03). No OAI. Alerts noted. Bioequivalence studies (single dose fasting and non-fasting) found acceptable 6/19/02. Dissolution studies also found acceptable. Bio studies were conducted by _____ (dosing) and _____ (analytical). These facilities have an acceptable OSI inspectional history. Office Level biowaiver 8/1/02. Revised "in vitro" dissolution specifications found acceptable 1/24/03. Office Level biowaiver 1/28/03. CMC found acceptable 4/9/03. Methods validation is pending - standard commitment has been received from Barr (1/25/02 amendment, page 6). Labeling found acceptable 4/9/02 (endorsed 4/28/03). First generic CMC review has been completed.

5. Robert L. West
Deputy Director, OGD

Date 5/9/2003
Initials Robert West

Para.IV Patent Cert: Yes☒ No☐; Pending Legal Action: Yes☒ No☐; Petition: Yes☐ No☒
Comments: Alleging Barr made paragraph IV certifications to both the '428 and '930 patents. Barr subsequently made a paragraph IV certification to the newly listed '715 pt. Barr was sued by KOS Pharmaceuticals on all three patents. Litigation ongoing.

This ANDA is recommended for tentative approval.

6. Gary Buehler
Director, OGD
Comments:

Date 5/9/2003
Initials Buehler

First Generic Approval ☒ PD or Clinical for BE ☐ Special Scientific or Reg.Issue ☐

7. Project Manager, Team 5 (Wanda Pamphile)
Date 5/9/03
Review Support Branch

Initials _____

N/A 5/8/03 Checked/RW
_____ Date PETS checked for first generic drug (just prior to notification to firm)

Applicant notification:
10:14 Time notified of approval by phone 10:17 Time approval letter faxed

FDA Notification:
5/9/03 Date e-mail message sent to "CDER-OGDAPPROVALS≅ distribution list.
6/9/03 Date Approval letter copied to \\CDS014\DRUGAPP\ directory.

:\reports\approval\approvrou2.doc

RECORD OF TELEPHONE CONVERSATION/MEETING

Called Barr and was connected to Mr. Ahmed, since Nick Tantillo was ———— today. Requested the following information prior to processing these two ANDA's from Tentative Approval to Final Approval.

First, we requested that the formerly accepted USP Chromatographic Impurity would have to be updated to ICH Q3A (R) and ICH Q3B (R) requirements for drug substance and drug product, respectively.

Secondly, Dr. Cai reviewed the dissolution test methodology using the ———— ———— ———— This was based on the previously submitted report in amendments to the subject ANDA's .

Mr. Ahmed indicated that he would consult the appropriate people in Barr to find out a proper response to our concerns and we indicated that Barr could respond by a telefax amendment to both of these ANDA's.

Mr. Ahmed thanked us for this information.

(end of memo)

DATE:
February 18, 2005

ANDA NUMBER:
76-250 (1000mg)
76-378 (500mg, 750mg)

IND NUMBER:
N/A

TELECON

INITIATED BY:
- ☐ **APPLICANT/SPONSOR**
- ■ **FDA**

MADE:
- ■ **BY TELEPHONE**
- ☐ **IN PERSON**

PRODUCT NAME:
Niacin ERT

FIRM NAME:
Barr Laboratories

NAME AND TITLE OF PERSON WITH WHOM CONVERSATION WAS HELD:
Sharif Ahmed

TELEPHONE NUMBER:
(201) 930-3650

SIGNATURE:
B.C. Cai 2/18/05
A.J. Mueller 2/18/05

V:\FIRMSAM\BARR\TELECONS\76250MEM.DOC

OGD APPROVAL ROUTING SUMMARY

ANDA # 76-250 Applicant: Barr Laboratories, Inc.
Drug: Niacin Extended Release Tablets Strength(s) 1000 mg

\PPROVAL ☒ TENTATIVE APPROVAL ☐ SUPPLEMENTAL APPROVAL (NEW STRENGTH) ☐ OTHER ☐

REVIEWER:	DRAFT Package	FINAL Package
1. Martin Shimer Chief, Reg. Support Branch	Date 4/20/05 Initials MS	Date _____ Initials _____

Contains GDEA certification: Yes ☑ No ☐ (required if sub after 6/1/92)
Determ. of Involvement? Yes ☐ No ☐
Pediatric Exclusivity System
RLD = NDA# _____
Patent/Exclusivity Certification: Yes ☑ No ☐
Date Checked _____
If Para. IV Certification- did applicant
Nothing Submitted ☐
Notify patent holder/NDA holder Yes ☑ No ☐
Written request issued ☐
Was applicant sued w/in 45 days: Yes ☑ No ☐
Study Submitted ☐
Has case been settled: Yes ☐ No ☑ Date settled:
Is applicant eligible for 180 day
Generic Drugs Exclusivity for each strength: Yes ☑ No ☐
Date of latest Labeling Review/Approval Summary ongoing
Any filing status changes requiring addition Labeling Review Yes ☐ No ☑
Type of Letter: Tentative for 180day exclusivity for All strengths & patents
Comments: 30 month stay for '428, '930 & '715 patents has expired
Barr sued 2° to '967 → NO 30 month stay as '967 is post MMA not sued on '229 or '691

2. Project Manager, _Ben Danso_ Team_5_ Review Support Branch	Date_3/31/05_ Initials_BD__	Date _____ Initials _____

Original Rec'd date_10/2/01_
EER Status Pending ☐ Acceptable ☒ OAI ☐
Date Acceptable for Filing_10/3/01_
Date of EER Status _2/23/05_
Patent Certification (type)_P IV_
Date of Office Bio Review _1/28/03_
Date Patent/Exclus.expires_____
☒ Date of Labeling Approv. Sum 4-7-05 (DC)
Citizens' Petition/Legal Case Yes☐ No ☐
Labeling Acceptable Email Rec'd Yes ☐ No ☐
(If YES, attach email from PM to CP coord)
Labeling Acceptable Email filed Yes ☐ No ☐
First Generic Yes ☒ No ☐ Date of Sterility Assur. App. _____
Methods Val. Samples Pending Yes ☐ No ☐
MV Commitment Rcd. from Firm Yes ☐ No ☐
Acceptable Bio reviews tabbed Yes ☒ No ☐
Modified-release dosage form: Yes ☒ No ☐
Suitability Petition/Pediatric Waiver
Interim Dissol. Specs in AP Ltr: Yes ☐
Pediatric Waiver Request Accepted ☐ Rejected ☐ Pending ☐
Previously reviewed and tentatively approved ☒ Date _5/9/03_
Previously reviewed and CGMP def. /NA Minor issued ☐ Date _____
Comments: Post Approval Commitment Tracking – To finalize Dissolution Specs. PACT Program Entry required

3. David Read **(PP IVs Only)** OGD Regulatory Counsel, Comments: see revised version.	Pre-MMA Language included ☑ Post-MMA Language Included ☑	Date 4/11/05 Initials DR

4. Div. Dir./Deputy Dir. Chemistry Div. I II OR III Comments:		Date 4/12/05 Initials RS

CMC OK
TA→AP

REVIEWER: FINAL ACTION

5. Frank Holcombe **First Generics Only** Date_____
Assoc. Dir. For Chemistry Initials_____
Comments: (First generic drug review)
N/A - this ANDA previously TA'd
RLD= Niaspan Tablets - NDA 20381 (003) of KOS Pharmaceuticals

6. Vacant Date_____
Deputy Dir., DLPS Initials_____

7. Peter Rickman Date 4/14/05
Director, DLPS Initials CV
Para.IV Patent Cert: Yes ☒ No ☐; Pending Legal Action: Yes ☒ No ☐; Petition: Yes ☐ No ☒
Comments:
✓EES acceptable on 2/23/05. ✓No OAI alerts pending. Application has an API manufacturer and a DP manufacturer plus testing sites entered.
✓Bio is acceptable for this ANDA. The studies have been found acceptable by DBE.
OR ✓Interim Dissolution specs were granted to the firm + have been incorporated into their ANDA. ✓These specs are accordingly in the AP letter. There are no DSI inspections pending. Bio was acceptable on 1/28/03 by D. Conner
✓FPL acceptable on 4/5/05 - J. Grace 4/4/05 PACT - To finalize Diss. Specs. ✓Pass
✓CMC acceptable on 3/15/05 - A. Mueller
✓MV commitment in 3/25/02 Amdt.
ANDA eligible for full AP ✓Pass 4/14/05

8. Robert L. West Date 4/14/05
Deputy Director, OGD Initials CV
Para.IV Patent Cert: Yes ☒ No ☐; Pending Legal Action: Yes ☐ No ☐; Petition: Yes ☐ No ☒
Comments:
✓Barr made a PIV cert to the '428 patent, and were sued > civil case 02-CV-1483
✓Barr made a PIV cert to the '930 patent, and were sued -30 month exp. 7/23/04
✓Barr filed a PIV cert to the '715 patent, and was sued - case - 02-CV-8995 - exp 3/30/05
✓Barr filed a PIV cert to the '967 and was sued - case 04-CV-2403 - post mmA -
✓Barr file a PIV cert to the '691 - not sued within 45 days
✓Barr filed a PIV cert to the '229 - not sued
✓Barr is Eligible for 180 day exclusivity and the Application is Approvable.

9. Gary Buehler Date 4/14/05
Director, OGD Initials Gill for
Comments:
First Generic Approval ☐ PD or Clinical for BE ☐ Special Scientific or Reg.Issue ☐

10. Project Manager, Team _Ben Danso__ Date 4/15/05
Review Support Branch Initials BD
_____Date PETS checked for first generic drug (just prior to notification to firm)
Applicant notification:
1:22 Time notified of approval by phone 1:25 Time approval letter faxed
FDA Notification:
4/15 Date e-mail message sent to "CDER-OGDAPPROVALS" distribution list.
4/15 Date Approval letter copied to \\CDS014\DRUGAPP\ directory.

File V:/division/dlps/approvrou9.doc

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 76-250

CORRESPONDENCE

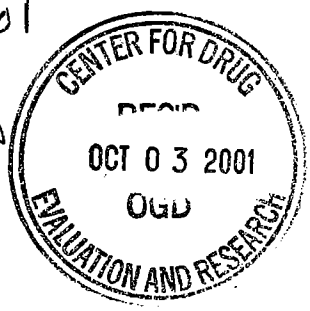
Barr Laboratories, Inc.

2 Quaker Road • P.O. Box 2900 • Pomona, NY 10970-0519 • 845/362-1100

October 2, 2001

505(b)(2) OK
26-NOV-2001

Office of Generic Drugs
Center for Drug Evaluation and Research
FOOD AND DRUG ADMINISTRATION
Document Control Room 150
Metro Park North II
7500 Standish Place
Rockville, Maryland 20855-2773



REFERENCE: ABBREVIATED NEW DRUG APPLICATION
Niacin Extended Release Tablets, 1000 mg

In accordance with the regulations under section 505(j) of the Federal Food and Cosmetic Act, Barr Laboratories, Inc. is submitting an Abbreviated New Drug Application for **Niacin Extended Release Tablets, 1000 mg.**

The application is provided in duplicate, as an archival copy, and a review copy. The archival copy of the application is contained in blue binders and consists of 10 volumes. The chemistry, manufacturing and controls part of the review copy is contained in red binders and consists of 2 volumes. Two additional review volumes each containing analytical methods section are also provided since the drug product is not a USP article. The bioequivalence part of the review copy is contained in an orange binder consisting of 7 volumes.

Included in this application and in accordance with the Generic Drug Enforcement Act of 1992, are Debarment Certification Statements from Barr and its outside contractors. Field Copies of this application have been forwarded to the New York and Baltimore District Offices.

Certifications of financial interests and arrangements of clinical investigators conducting the bioequivalence study are provided in Section VI.

The BA/BE section of this application will be provided in electronic format within 30 days from this date. Barr Laboratories, Inc. will, at that time, provide a declaration that the information in the electronic submission is the same as the information provided in the paper submission.

The format of this application is in accordance with Office of Generic Drug's Guidance for Industry: Organization of an ANDA, dated February 1999. The information submitted in this application is also in accordance with the October 14, 1994 communication from Dr. Janet Woodcock, (CDER) and Mr. Ronald Chesemore (ORA).

If you have any questions concerning this application, please contact me by phone at (845) 353-8432 or by fax at (845) 353-3859. Your earliest acknowledgment to this application will be very much appreciated.

Sincerely,

BARR LABORATORIES, INC.

Christine Mundkur
Vice President, Quality and
Regulatory Counsel

76-250

Barr Laboratories, Inc.

2 Quaker Road • P.O. Box 2900 • Pomona, NY 10970-0519 • 845/362-1100

October 3, 2001

Office of Generic Drugs
Center for Drug Evaluation and Research
FOOD AND DRUG ADMINISTRATION
Document Control Room 150
Metro Park North II
7500 Standish Place
Rockville, Maryland 20855-2773

NC

NEW CORRESP

GENERAL CORRESPONDENCE

REFERENCE: **Pending Abbreviated New Drug Application**
Niacin Extended Release Tablets, 1000 mg

Reference is made to Barr's pending Abbreviated New Drug Application ("ANDA") dated October 2, 2001 submitted under Section 505(j) of the Federal Food, Drug and Cosmetic Act for **Niacin Extended Release Tablets, 1000 mg.**

Barr inadvertently did not submit the following documents with the Pending Abbreviated New Drug Application for Niacin Extended Release Tablets, 1000 mg:

- Form 356h, Application to Market a New Drug, Biologic, or an Antibiotic Drug for Human Use
- Establishment Information Tables
- Cross Reference List

Enclosed please find these documents. We apologize for any inconvenience that this may have caused.

If you have any questions concerning this application, please contact me by phone at (845) 353-8432 or by fax at (845) 353-3859. Your earliest acknowledgment to this application will be very much appreciated.

Sincerely,

BARR LABORATORIES, INC.

Christine Mundkur
Vice President, Quality and
Regulatory Counsel

CENTER FOR DRUG EVALUATION AND RESEARCH
OCT 05 2001

ANDA 76-250

NOV 26 2001

Barr Laboratories, Inc.
Attention: Christine Mundkur
2 Quaker Road
P.O. Box 2900
Pomona, NY 10970

Dear Madam:

We acknowledge the receipt of your abbreviated new drug application submitted pursuant to Section 505(j) of the Federal Food, Drug and Cosmetic Act. Reference is made to the correspondence dated October 3, 2001.

NAME OF DRUG: Niacin Extended-release Tablets, 1000 mg

DATE OF APPLICATION: October 2, 2001

DATE (RECEIVED) ACCEPTABLE FOR FILING: October 3, 2001

You have filed a Paragraph IV patent certification, in accordance with 21 CFR 314.94(a)(12)(i)(A)(4) and Section 505(j)(2)(A)(vii)(IV) of the Act. Please be aware that you need to comply with the notice requirements, as outlined below. In order to facilitate review of this application, we suggest that you follow the outlined procedures below:

28-NOV-2001

CONTENTS OF THE NOTICE

You must cite section 505(j)(2)(B)(ii) of the Act in the notice and should include, but not be limited to, the information as described in 21 CFR 314.95(c).

SENDING THE NOTICE

In accordance with 21 CFR 314.95(a):

- Send notice by U.S. registered or certified mail with return receipt requested to each of the following:

  1) Each owner of the patent or the representative designated by the owner to receive the notice;

2) The holder of the approved application under section 505(b) of the Act for the listed drug claimed by the patent and for which the applicant is seeking approval.

3) An applicant may rely on another form of documentation only if FDA has agreed to such documentation in advance.

DOCUMENTATION OF NOTIFICATION/RECEIPT OF NOTICE

You must submit an amendment to this application with the following:

- In accordance with 21 CFR 314.95(b), provide a statement certifying that the notice has been provided to each person identified under 314.95(a) and that notice met the content requirements under 314.95(c).

- In accordance with 21 CFR 314.95(e), provide documentation of receipt of notice by providing a copy of the return receipt or a letter acknowledging receipt by each person provided the notice.

- A designation on the exterior of the envelope and above the body of the cover letter should clearly state "PATENT AMENDMENT". This amendment should be submitted to your application as soon as documentation of receipt by the patent owner and patent holder is received.

DOCUMENTATION OF LITIGATION/SETTLEMENT OUTCOME

You are requested to submit an amendment to this application that is plainly marked on the cover sheet "PATENT AMENDMENT" with the following:

- If litigation occurs within the 45-day period as provided for in section 505(j)(4)(B)(iii) of the Act, we ask that you provide a copy of the pertinent notification.

- Although 21 CFR 314.95(f) states that the FDA will presume the notice to be complete and sufficient, we ask that if you are not sued within the 45-day period, that you provide a letter immediately after the 45 day period elapses, stating that no legal action was taken by each person provided notice.

- You must submit a copy of a court order or judgement or a settlement agreement between the parties, whichever is applicable, or a licensing agreement between you and the patent holder, or any other relevant information. We ask that this information be submitted promptly to the application.

If you have further questions you may contact Gregg Davis, Chief, Regulatory Support Branch, at (301) 827-5862.

We will correspond with you further after we have had the opportunity to review the application.

Please identify any communications concerning this application with the ANDA number shown above.

Should you have questions concerning this application, contact:

Michelle Dillahunt
Project Manager
(301) 827-5848

Sincerely yours,

Gregory S. Davis for

Wm Peter Rickman
Acting Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

cc: ANDA 76-250
DUP/Jacket
Division File
Field Copy
HFD-610/R.West
HFD-610/P.Rickman
HFD-92
HFD-615/M.Bennett
HFD-600/

Endorsement: HFD-615/GDavis, Chief, RSB date
HFD-615/BFritsch, CSO date
Word File
V:/FIRMSam/barr/ltrs&rev/76250.ack
FT/
ANDA Acknowledgment Letter!

26-NOV-2001

11/26/01

APPEARS THIS WAY
ON ORIGINAL

N 76-250

Barr Laboratories, Inc.

ELECTRONIC BA/BE SUBMISSION ENCLOSED

BIOAVAILABILITY

November 6, 2001

NEW CORRESP

NC

Office of Generic Drugs
CDER FDA
Metro Park North II
7500 Standish Place
Rockville, MD 20855

REFERENCE: ABBREVIATED NEW DRUG APPLICATION
Niacin Extended Release Tablets, 1000mg

Reference is made to our Abbreviated New Drug Application which was submitted on October 2, 2001 pursuant to Section 505(j) of the Federal Food, Drug and Cosmetic Act for Niacin Extended Release Tablets, 1000mg.

We have prepared an electronic submission of the bioequivalence data for the referenced product using FDA's Electronic Validation Application (EVA) version 4.14, and we are submitting the information for use during review of our ANDA for Niacin Extended Release Tablets, 1000mg. Information regarding the following studies is contained on two 3½" diskettes (1 original, 1 copy).

Report Number	Title
10116201	The Effect of Food on the Relative Bioavailability of Two Niacin Formulations
10016214	The Relative Bioavailability of Two Niacin Formulations Under Fasting Conditions

We certify that the data that is submitted electronically is identical to the data contained in the hard copy submission.

If you need any clarification of the information provided, or additional data, please feel free to contact me at (845) 348 - 6845.

Sincerely,

Linda O'Dea

Linda O'Dea
Associate Director
Regulatory Affairs

CENTER FOR DRUG EVALUATION AND RESEARCH
NOV 09 2001
OGD

Barr Laboratories, Inc.

2 Quaker Road • P.O. Box 2900 • Pomona, NY 10970-0519 • 845/362-1100

November 21, 2001

Office of Generic Drugs
Center for Drug Evaluation and Research
FOOD AND DRUG ADMINISTRATION
Document Control Room 150
Metro Park North II
7500 Standish Place
Rockville, Maryland 20855-2773

76-250

NEW CORRESP
NC

AMENDMENT TO PENDING APPLICATION

REFERENCE: **Abbreviated New Drug Application**
NIACIN EXTENDED RELEASE TABLETS, 1000 MG

Reference is made to Barr's pending Abbreviated New Drug Application ("ANDA") dated October 2, 2001 submitted under Section 505(j) of the Federal Food, Drug and Cosmetic Act for Niacin Extended Release Tablets, 1000 mg.

At this time Barr is submitting a Second Addendum to the Method Validation of Niacin and Nicotinuric Acid in Human Plasma, [redacted] 038.100A, composed by [redacted] dated October 8, 2001. This addends Report Number: V0105017 — of Bio-Study # 10116201, The Effect of Food on the Relative Bioavailability of Two Niacin Formulations and Bio-Study # 10016214, The Relative Bioavailability of Two Niacin Formulations Under Fasting Conditions.

An identical copy of this Amendment has been provided to the New York and Baltimore District Field Offices. A document certification is attached. If you have any questions, please contact me by phone at (845) 353-8432 or by fax at (845) 353-3859.

Sincerely,

BARR LABORATORIES, INC.

Christine Mundkur
Senior Vice President, Quality and Regulatory Counsel

cc: New York and Baltimore District Field Offices

MINOR AMENDMENT

ANDA 76-250

FEB 20 2002

OFFICE OF GENERIC DRUGS, CDER, FDA
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773 (301-594-0320)

TO: APPLICANT: Barr Laboratories, Inc. TEL: 845-353-8432

ATTN: Christine Mundkur FAX: 845-353-3859

FROM: Michelle Dillahunt PROJECT MANAGER: 301-827-5848

Dear Madam:

This facsimile is in reference to your abbreviated new drug application dated October 2, 2001, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Niacin Extended Release Tablets, 1000 mg.

The application is deficient and, therefore, Not Approvable under Section 505 of the Act for the reasons provided in the attachments (3 pages). This facsimile is to be regarded as an official FDA communication and unless requested, a hard copy will not be mailed.

The file on this application is now closed. You are required to take an action described under 21 CFR 314.120 which will either amend or withdraw the application. Your amendment should respond to all of the deficiencies listed. Facsimiles or partial replies will not be considered for review, nor will the review clock be reactivated until all deficiencies have been addressed. The response to this facsimile will be considered to represent a MINOR AMENDMENT and will be reviewed according to current OGD policies and procedures. The designation as a MINOR AMENDMENT should appear prominently in your cover letter. You have been/will be notified in a separate communication from our Division of Bioequivalence of any deficiencies identified during our review of your bioequivalence data. If you have substantial disagreement with our reasons for not approving this application, you may request an opportunity for a hearing.

SPECIAL INSTRUCTIONS: Chemistry and Labeling comments included.

2/20/02 MD

Redacted 1 page(s)

of trade secret and/or

confidential commercial

information from

2/20/2002 FDA FAX

8. [ ]

B. In addition to responding to the deficiencies presented above, please note and acknowledge the following comments in your response:

1. All facilities referenced in the ANDA should have a satisfactory compliance evaluation at the time of approval. We have requested an evaluation from the Office of Compliance.

2. Your Bioequivalence information is pending review. Deficiencies, if any, will be communicated separately.

3. Labeling deficiencies will also need to be addressed in your reply.

4. We require an acceptable Methods Validation to support the ANDA and we are currently scheduling the study. Please provide samples promptly when contacted. Please also provide a commitment to work with us to expeditiously resolve any deficiencies from the Methods Validation study if the ANDA is approved prior to its completion.

5. Please provide any additional long term stability data that may be available.

6. You have not provided the Paragraph IV information specified in our acknowledgement letter dated November 26, 2001.

Sincerely yours,

Rashmikant M. Patel, Ph.D.
Director
Division of Chemistry I
Office of Generic Drugs
Center for Drug Evaluation and Research

REVIEW OF PROFESSIONAL LABELING#1
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH

ANDA Number: **76-250** Date of Submission: October 2, 2001
Applicant's Name: Barr
Established Name: **Niacin Extended-release Tablets 1000 mg**

Labeling Deficiencies:

1. CONTAINER - Revise the Each tablet contains statement as folllows:

   Each Extended-release tablet contains 1000 mg niacin.

2. .PROFESSIONAL INSERT - Satisfactory in draft.

Please revise your labels and labeling, as instructed above, and submit 12 final printed labels and labeling or draft labeling if you prefer.

Prior to approval, it may be necessary to further revise your labeling subsequent to approved changes for the reference listed drug. We suggest that you routinely monitor the following website for any approved changes - http://www.fda.gov/cder/ogd/rld/labeling_review_branch.html

To facilitate review of your next submission, and in accordance with 21 CFR 314.94(a)(8)(iv), please provide a side-by-side comparison of your labeling with your last submission with all differences annotated and explained.

John D Grunfeld

Wm. Peter Rickman
Acting Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

Barr Laboratories, Inc.

2 Quaker Road • P.O. Box 2900 • Pomona, NY 10970-0519 • 845/362-1100

March 4, 2002

NEW CORRESP
NC

Office of Generic Drugs
Center for Drug Evaluation and Research
FOOD AND DRUG ADMINISTRATION
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, Maryland 20855-2773

PATENT AMENDMENT

REFERENCE: **ANDA 76-250**
NIACIN EXTENDED RELEASE TABLETS, 1000MG

Reference is made to our Pending Abbreviated New Drug Application submitted under Section 505(j) of the Federal Food, Drug and Cosmetic Act for Niacin Extended Release Tablets, 1000 mg.

In accordance with our Patent Certification Statement submitted in Section III of the Application and 21 CFR §314.95(a), notice was sent on January 15, 2002 by certified mail, return receipt requested to the owner of the patents claimed and the holder of the approved application under Section 505(b) of the Act.

In accordance with 21 CFR §314.95(b), Barr is hereby submitting a Patent Amendment to certify that notice was provided to KOS Pharmaceuticals, Inc. (U.S patent owner) by Sterne, Kessler, Goldstein & Fox, P.L.L.C. on behalf of Barr Laboratories. These letters were sent upon receipt of FDA's acknowledgement letter dated April 26, 2001 stating that Barr's Abbreviated New Drug Application was sufficiently complete to permit a substantive review.

The contents of the notice letter comply with 21 CFR §314.95(c). The notice letter cites Section 505(j)(2)(B)(ii) of the act and informs all parties of the factual and legal basis for asserting that the U.S. Patent Nos. 6080428 and 6129930 held by KOS Pharmaceuticals, Inc. are invalid, unenforceable or will not be infringed by the manufacture, use or sale of Barr's Niacin Extended Release Tablets, 1000 mg.

In accordance with 21 CFR §314.95(e), enclosed is a copy of the return receipt for the notice that was delivered on January 23, 2002.

This completes Barr's Patent Amendment dated March 1, 2002.

Sincerely,

BARR LABORATORIES, INC.

Christine Mundkur
Senior Vice President,
Quality and Regulatory Counsel

CENTER FOR DRUG EVALUATION AND RESEARCH
MAR 05 2002

Barr Laboratories, Inc.

2 Quaker Road • P.O. Box 2900 • Pomona, NY 10970-0519 • 845/362-1100

NTI
NTR 3-28-02

March 22, 2002

Office of Generic Drugs
Center for Drug Evaluation and Research
FOOD AND DRUG ADMINISTRATION
Document Control Room 150
Metro Park North II
7500 Standish Place
Rockville, Maryland 20855-2773

NC
NEW CORRESP

PATENT AMENDMENT

REFERENCE: **ANDA # 76-250**
NIACIN EXTENDED RELEASE TABLETS, 1000 MG

In accordance with the regulations under section 505(j) of the Federal Food and Cosmetic Act, Barr Laboratories, Inc. has submitted an Abbreviated New Drug Application for Niacin Extended Release Tablets, 1000 mg.

In accordance with your acknowledgement of receipt letter dated November 26, 2001, Barr is hereby submitting a Patent Amendment to certify that Barr Laboratories Inc. has received notice of litigation from KOS Pharmaceuticals, Inc. (NDA holder and U.S. patent owner of record) within the 45-day period as provided for in section 505 (j)(4)(B)(iii) of the Act. The case KOS Pharmaceuticals vs. Barr Laboratories, Inc, Civil Action No.: 02-CV-1683 in the U.S. District Court, Southern District of New York was originally filed on March 7, 2001 and amended on March 11, 2002. Further, Barr agrees to submit a copy of the court order or judgement or settlement agreement between Barr and KOS Pharmaceutical or a licensing agreement between Barr and the patent holder or any other relevant information.

If you have any questions concerning this patent amendment, please contact me by phone at (845) 353-8432 or by fax at (845) 353-3859.

Sincerely,

BARR LABORATORIES, INC.

Christine Mundkur
Senior Vice President, Quality and
Regulatory Counsel

RECEIVED

MAR 2 5 2002

OGD / CDER

Barr Laboratories, Inc.

2 Quaker Road • P.O. Box 2900 • Pomona, NY 10970-0519 • 845/362-1100

March 25, 2002

Office of Generic Drugs
Center for Drug Evaluation and Research
FOOD AND DRUG ADMINISTRATION
Document Control Room 150
Metro Park North II
7500 Standish Place
Rockville, Maryland 20855-2773

ORIG AMENDMENT
N/AM / DRFT LBL

MINOR AMENDMENT

REFERENCE: **ANDA 76-250**
NIACIN EXTENDED RELEASE TABLETS, 1000 mg

Reference is made to Barr's pending Abbreviated New Drug Application ("ANDA") dated October 2, 2001 submitted under Section 505(j) of the Federal Food, Drug and Cosmetic Act for Niacin Extended Release Tablets, 1000 mg.

Reference is also made to the Agency's minor deficiency letter dated February 20, 2002. The deficiencies identified in the February 20, 2002 letter and our responses are as follows:

A. DEFICIENCIES:

COMMENT 1:

In the column of "PHARMACEUTICAL CATEGORY" of your Form 356h, it says the drug is "used for the treatment of ———— '. Please clarify.

RESPONSE:

Barr inadvertently stated the incorrect "Indication for Use". The correct "Indication for Use" is "An adjunct to diet for treating hyperlipidemia."

COMMENT 2:

[ ]

RESPONSE:

[ ] is provided in Attachment I.

RECEIVED
MAR 26 2002
OGD / CDER

Redacted 4 page(s)

of trade secret and/or

confidential commercial

information from

- 3/25/2002 BARR LETTER

2. **Your Bioequivalence information is pending review. Deficiencies, if any, will be communicated separately.**

   RESPONSE

   Barr acknowledges that the Bioequivalence information is pending review. Deficiencies, if any, will be communicated separately.

3. **Labeling deficiencies will also need to be addressed in your reply.**

   RESPONSE:

   Barr has addressed the labeling deficiencies. Please see Attachment VI for details.

4. **We require an acceptable Methods Validation to support the ANDA and we are currently scheduling the study. Please also provide a commitment to work with us to expeditiously resolve any deficiencies from the Methods Validation study if the ANDA is approved prior to its completion.**

   RESPONSE:

   Barr commits to work with the Agency to expeditiously resolve any deficiencies from the Methods Validation study if the ANDA is approved prior to its completion

5. **Please provide any additional long-term stability data that may be available.**

   RESPONSE:

   As requested by the Agency, additional long-term stability data through twelve months of storage is provided in Stability Report ARD_RPT-168. Please find Stability Report ARD_RPT-168 as Attachment V.

6. **You have not provided the Paragraph IV information specified in our acknowledgement letter dated November 26, 2001.**

   RESPONSE:

   On March 4, 2002, Barr submitted a Patent Amendment, including a copy of the return receipt, certifying that notice was given to KOS Pharmaceuticals, Inc. (the patent holder) concerning the filing of Barr's application. On March 22, 2002, Barr filed another Patent Amendment to certify that Barr received notice of litigation from KOS Pharmaceuticals, Inc.

Labeling Deficiencies

1. **CONTAINER- Revise the Each tablet contains statement as follows:**
   Each Extended-release tablet contains 1000 mg niacin.

   RESPONSE:

   Acknowledged. Barr has incorporated the change into it's labeling. Please see ATTACHMENT VI for revised labels.

2. **PROFESSIONAL INSERT- Satisfactory in draft.**

RESPONSE:

Acknowledged.

Please revise your labels and labeling, as instructed above, and submit 12 final printed labels and labeling or draft labeling if you prefer.

RESPONSE:

Acknowledged. Please see ATTACHMENT VI for revised draft labels.

Prior to approval, it may be necessary to further revise your labeling subsequent to approved changes for the reference listed drug. We suggest that you routinely monitor the following website for any approved changes - http://www.fda.gov/cder/ogd/rid/labeling_review_branch.html

RESPONSE:

Acknowledged.

To facilitate review of your next submission, and in accordance with 21 CFR 314.94(a)(8)(iv), please provide a side-by-side comparison of your labeling with your last submission with all differences annotated and explained.

RESPONSE:

Acknowledged.

An identical copy of this Amendment has been provided to the New York and Baltimore District Offices. A document certification is attached.

This completes the Minor Amendment. If you have any questions, please contact me by phone at (845) 353-8432 or by fax at (845) 353-3859.

Sincerely,

BARR LABORATORIES, INC.

Pete Baer for

Christine Mundkur
Senior Vice President, Quality and Regulatory Counsel

BIOEQUIVALENCY AMENDMENT

ANDA 76-250

MAY - 3 2002

OFFICE OF GENERIC DRUGS, CDER, FDA
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773 (301-594-0320)

TO: APPLICANT: Barr Laboratories, Inc. TEL: 845-362-1100

ATTN: Christine Mundkur FAX: 845-353-3859

FROM: Krista M. Scardina, Pharm.D. PROJECT MANAGER: 301-827-5847

Dear Ms. Mundkur:

This facsimile is in reference to the bioequivalency data submitted on October 2, 2001, pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Niacin Extended-Release Tablets, 1000 mg.

The Division of Bioequivalence has completed its review of the submission(s) referenced above and has identified deficiencies which are presented on the attached __1___ pages. This facsimile is to be regarded as an official FDA communication and unless requested, a hard-copy will not be mailed.

You should submit a response to these deficiencies in accord with 21 CFR 314.96. Your amendment should respond to all the deficiencies listed. **Facsimiles or partial replies will not be considered for review**, nor will the review clock be reactivated until all deficiencies have been addressed. Your cover letter should clearly indicate that the response is a "Bioequivalency Amendment" and clearly identify any new studies (i.e., fasting, fed, multiple dose, dissolution data, waiver or dissolution waiver) that might be included for each strength. We also request that you include a copy of this communication with your response. Please direct any questions concerning this communication to the project manager identified above.

SPECIAL INSTRUCTIONS:

KS

A1.1 Ack
Bing

MAY - 3 2002

BIOEQUIVALENCY COMMENTS TO BE PROVIDED TO THE APPLICANTS

ANDA: 76-250 APPLICANT: Barr Laboratories, Inc.

DRUG PRODUCT: Niacin Extended Release Tablets, 1000 mg

The Division of Bioequivalence has completed its review of your submission acknowledged on the cover sheet. The following deficiencies have been identified:

You have submitted a long-term frozen stability study covering a period of 78 days only. However, the overall storage periods for the plasma niacin and nicotinuric acid samples are 150 and 179 days, respectively for the fasting and non-fasting studies. Therefore, analytical method validations for niacin and nicotinuric acid are deficient, and the biostudies under fasting and non-fasting conditions are incomplete.

The in vitro dissolution testing conducted on your niacin extended release tablets, 1000 mg is incomplete. The Division recommends that you conduct additional dissolution testing using the following conditions:

Apparatus: USP Apparatus 1 (basket), 100 rpm
Medium: Buffer pH 1.2, 4.5 and 6.8, 900 mL
No. of Sampling Units: 12
Sampling Time: 1,3,6,9,12,20 and 24 hours.

Please also submit similarity factor f2 between the test and reference products.

Sincerely yours,

Dale P. Conner

Dale P. Conner, Pharm.D.
Director, Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

Barr Laboratories, Inc.

2 Quaker Road • P.O. Box 2900 • Pomona, NY 10970-0519 • 845/362-1100

May 17, 2002

ORIG AMENDMENT
N/A B

Office of Generic Drugs
Center for Drug Evaluation and Research
FOOD AND DRUG ADMINISTRATION
Document Control Room 150
Metro Park North II
7500 Standish Place
Rockville, Maryland 20855-2773

REFERENCE: **ANDA 76-250**
Niacin Extended Release Tablets, 1000 mg
BIOEQUIVALENCY AMENDMENT

Reference is made to our Abbreviated New Drug Application submitted under Section 505(j) of the Federal Food, Drug and Cosmetic Act for **Niacin Extended Release Tablets, 1000 mg** dated October 2, 2001.

Reference is also made to the Agency's letter dated May 3, 2002 regarding Barr's application in which the following deficiencies are stated:

COMMENT 1:

You have submitted a long-term frozen stability study covering a period of 78 days only. However, the overall storage periods for the plasma niacin and nicotinuric acid samples are 150 and 179 days, respectively for the fasting and non-fasting studies. Therefore, analytical method validations for niacin and nicotinuric acid are deficient, and biostudies under fasting and non-fasting conditions are incomplete.

RESPONSE 1:

In Attachment I, please find the Second Addendum to the Method Validation of Niacin and Nicotinuric Acid in Human Plasma, [redacted] 038.100A. This Addendum documents the long-term freezer stability of niacin and nicotinuric acid in human plasma over a period of one hundred and eighty-three days. This Addendum applies to both the fasting and food studies (protocol no.'s 10016214 and 10116201).

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MAY 2 0 2002
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COMMENT 2;

The in vitro dissolution testing conducted on your niacin extended release tablets, 1000 mg is incomplete. The Division recommends that you conduct additional dissolution testing using the following conditions:

Apparatus:	USP Apparatus 1 (basket), 100 rpm
Medium:	Buffer pH 1.2, 4.5 and 6.8, 900 mL
No. of Sampling Units:	12
Sampling Time:	1, 3, 6, 9, 12, 20 and 24 hours.

Please also submit similarity factor f2 between the test and reference products.

RESPONSE 2:

As requested by the Agency, Barr has conducted additional in vitro dissolution testing using the recommended conditions. The dissolution profile data tables, charts and similarity factors can be found in Attachment II.

An identical copy of this Amendment has been provided to the New York and Baltimore District Offices. A document certification is attached.

If you have any questions concerning this bioequivalency amendment, please contact me by phone at (845) 353-8432 or by fax at (845) 353-3859.

Sincerely,

BARR LABORATORIES, INC.

Christine Mundkur
Senior Vice President, Quality and
Regulatory Counsel

DEPARTMENT OF HEALTH AND
HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
OFFICE OF GENERIC DRUGS
7500 STANDISH PLACE, ROOM 150
ROCKVILLE, MD 20855-2773

Fax

NICK TANTILLO

To: ~~Christine Mundkur~~

Barr Laboratories, Inc.

From: Peter Chen

Phone: 845-353-8432

Fax: 845-353-3859

Phone: (301) 827-5848

Date: 08/12/02

Re: ANDA 76-250

Niacin Extended Release Tablets,

1000 mg

CC:

☐ **Urgent** ☐ **For Review** ☐ **Please Comment** ☐ **Please Reply** ☐ **Please Recycle**

- **Comments:**

Bioequivalency comments included.

TOTAL NUMBER OF PAGES ___1____

BIOEQUIVALENCY COMMENTS TO BE PROVIDED TO THE APPLICANTS

ANDA: 76-250 APPLICANT: Barr Laboratories, Inc.

DRUG PRODUCT: Niacin Extended Release Tablets, 1000 mg

The Division of Bioequivalence has completed its review of your submission acknowledged on the cover sheet, and has no further questions at this time.

We acknowledge that the following dissolution testing has been incorporated into your manufacturing controls and stability program:

The dissolution testing should be conducted in 900 mL of water at 37 ºC using USP apparatus I (basket) at 100 rpm. The test products should meet the following interim specifications:

Time (Hours)	Amount Dissolved (%)
1	**Not More Than —%**
3	Between ——— %
6	Between ——— %
9	Between ——— %
12	Between ——— %
20	**Not Less Than —— %**

Please note that the bioequivalency comments provided in this communication are preliminary. These comments are subject to revision after review of the entire application, upon consideration of the chemistry, manufacturing and controls, microbiology, labeling, or other scientific or regulatory issues. Please be advised that these regulatory reviews may result in the need for additional bioequivalency information and/or studies, or may result in a conclusion that the proposed formulation is not approvable.

Sincerely yours,

Dale P. Conner, Pharm.D.
Director, Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

Barr Laboratories, Inc.

2 Quaker Road • P.O. Box 2900 • Pomona, NY 10970-0519 • 845/362-1100

August 29, 2002

NEW CORRESP NAI 12/16/02
NC
PIV: 6,406,715
Rec'd by FDA Agency: 7/18/02

Office of Generic Drugs
Center for Drug Evaluation and Research
FOOD AND DRUG ADMINISTRATION
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, Maryland 20855-2773

PATENT AMENDMENT

REFERENCE: **ANDA 76-250**
NIACIN EXTENDED RELEASE TABLETS, 1000 MG

Reference is made to our Pending Abbreviated New Drug Application submitted under Section 505(j) of the Federal Food, Drug and Cosmetic Act for Niacin Extended Release Tablets, 1000 mg submitted on October 2, 2001.

Barr is hereby submitting a supplemental Paragraph IV Certification for Niacin Extended Release Tablets, 1000 mg. The Paragraph IV Certification has been revised to provide for a patent newly listed in the *Approved Drug Products with Therapeutic Equivalence (Orange Book)*. The newly listed patent is U.S. Patent No. 6,406,715.

Barr Laboratories, Inc. will give notice under 21 CFR § 314.95(a) to KOS Pharmaceuticals Inc., the NDA holder and the owner(s) of U.S. Patent No. 6,406,715, supplementing the patent certification for Barr's Abbreviated New Drug Application for Niacin Extended Release Tablets, 1000 mg to include a Paragraph IV Certification for U.S. Patent 6,406,715.

As provided in ANDA 76-250 at page 03-2, Barr Laboratories, Inc., on October 2, 2001 provided a Paragraph IV Certification for the two patents listed in the Orange Book at that time, U.S. Patent Nos. 6,080,428 and 6,129,930. Barr Laboratories, Inc. has already notified KOS Pharmaceuticals, Inc., according to the requirements of 21 CFR § 314.95(a) and (c), regarding the filing of ANDA 76-250 containing a Paragraph IV Certification for these two patents.

If you have any questions concerning this application, please contact me by phone at (845) 348-8051 or by fax at (845) 353-3859.

Sincerely,

BARR LABORATORIES, INC.

Nicholas Tantillo
Senior Director of Regulatory Affairs

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AUG 30 2002
OGD / CDER

NAI 9/11/02 E Thomas

Barr Laboratories, Inc.

2 Quaker Road • P.O. Box 2900 • Pomona, NY 10970-0519 • 845/362-1100

August 30, 2002

NEW CORRESP
NC

NAL - 5/24/03
PID - submitted on 8/30/02 is valid. P.M.P

Office of Generic Drugs
Center for Drug Evaluation and Research
FOOD AND DRUG ADMINISTRATION
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, Maryland 20855-2773

PATENT AMENDMENT

REFERENCE: **ANDA 76-250**
NIACIN EXTENDED RELEASE TABLETS, 1000 MG

Reference is made to our Pending Abbreviated New Drug Application submitted under Section 505(j) of the Federal Food, Drug and Cosmetic Act for Niacin Extended Release Tablets, 1000 mg submitted on October 2, 2001.

Barr is hereby submitting a supplemental Paragraph IV Certification for Niacin Extended Release Tablets, 1000 mg. The Paragraph IV Certification has been revised to provide for a patent newly listed in the *Approved Drug Products with Therapeutic Equivalence (Orange Book)*. The newly listed patent is U.S. Patent No. 6,406,715.

Barr Laboratories, Inc. will give notice under 21 CFR § 314.95(a) to KOS Pharmaceuticals Inc., the NDA holder and the owner(s) of U.S. Patent No. 6,406,715, supplementing the patent certification for Barr's Abbreviated New Drug Application for Niacin Extended Release Tablets, 1000 mg to include a Paragraph IV Certification for U.S. Patent 6,406,715.

As provided in ANDA 76-250 at page 03-2, Barr Laboratories, Inc., on October 2, 2001 provided a Paragraph IV Certification for the two patents listed in the Orange Book at that time, U.S. Patent Nos. 6,080,428 and 6,129,930. Barr Laboratories, Inc. has already notified KOS Pharmaceuticals, Inc., according to the requirements of 21 CFR § 314.95(a) and (c), regarding the filing of ANDA 76-250 containing a Paragraph IV Certification for these two patents.

If you have any questions concerning this application, please contact me by phone at (845) 348-8051 or by fax at (845) 353-3859.

Sincerely,

BARR LABORATORIES, INC.

Nicholas Tantillo
Senior Director of Regulatory Affairs

NC 9-12-02

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SEP 0 3 2002
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MINOR AMENDMENT

ANDA 76-250

OFFICE OF GENERIC DRUGS, CDER, FDA
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773 (301-594-0320)

OCT - 7 2002

TO: APPLICANT: Barr Laboratories, Inc. TEL: 845-353-8432

ATTN: Christine Mundkur FAX: 845-353-3859

FROM: Wanda Pamphile PROJECT MANAGER: 301-827-5848

Dear Madam:

This facsimile is in reference to your abbreviated new drug application dated October 2, 2001, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Niacin Extended Release Tablets, 1000 mg.

Reference is also made to your amendment(s) dated: March 25, 2002.

The application is deficient and, therefore, Not Approvable under Section 505 of the Act for the reasons provided in the attachments (1 page). This facsimile is to be regarded as an official FDA communication and unless requested, a hard copy will not be mailed.

The file on this application is now closed. You are required to take an action described under 21 CFR 314.120 which will either amend or withdraw the application. Your amendment should respond to all of the deficiencies listed. Facsimiles or partial replies will not be considered for review, nor will the review clock be reactivated until all deficiencies have been addressed. The response to this facsimile will be considered to represent a MINOR AMENDMENT and will be reviewed according to current OGD policies and procedures. The designation as a MINOR AMENDMENT should appear prominently in your cover letter. You have been/will be notified in a separate communication from our Division of Bioequivalence of any deficiencies identified during our review of your bioequivalence data. If you have substantial disagreement with our reasons for not approving this application, you may request an opportunity for a hearing.

SPECIAL INSTRUCTIONS:
Chemistry comments included.

WP 10/7/02

Redacted 1 page(s)

of trade secret and/or

confidential commercial

information from

10/7/2002 FDA FAX

Barr Laboratories, Inc.

2 Quaker Road • P.O. Box 2900 • Pomona, NY 10970-0519 • 845/362-1100

December 9, 2002

NFI: 12/16/02
Sued: 02-CV-8995
-No copy of RR by last
post office.
NEW CORRESP - Sued on 715 patent.
NC
P.M.D

Office of Generic Drugs
Center for Drug Evaluation and Research
FOOD AND DRUG ADMINISTRATION
Document Control Room 150
Metro Park North II
7500 Standish Place
Rockville, Maryland 20855-2773

PATENT AMENDMENT

REFERENCE: **ANDA # 76-250**
NIACIN EXTENDED RELEASE TABLETS, 1000 MG

Reference is made to our abbreviated new drug application submitted pursuant to section 505(j) of the Federal Food and Cosmetic Act for Niacin Extended Release Tablets, 1000 mg.

Reference is also made to our August 29, 2002 patent amendment for a supplemental paragraph IV certification. In accordance with 21 CFR 314.95 (b) Barr certifies that the required notice under 21 CFR 314.95 (a) was provided to KOS Pharmaceuticals Inc., the NDA holder and the owner of the newly listed patent 6,406,715. Unfortunately, it appears that the US Postal Services lost the delivery receipt that was supposed to be returned to Barr. However, upon receipt of Barr's notice KOS Pharmaceuticals filed a complaint to the U.S. District Court of Southern District of New York (copy attached). Please note that item 11 on page of the complaint confirms that Barr sent KOS a notification dated September 27, 2002 and that KOS received the notice on September 30, 2002.

RR *

Barr is submitting this Patent Amendment to inform you that Barr has received notice of litigation from KOS Pharmaceuticals, Inc. (NDA holder and U.S. patent owner of record) within the 45-day period as provided for in section 505 (j)(4)(B)(iii) of the Act. Further, Barr agrees to submit a copy of a court order or judgement or settlement agreement between Barr and KOS Pharmaceuticals, whichever is applicable, or a licensing agreement between Barr and the patent holder or any other relevant information.

Please note that the case KOS Pharmaceuticals vs. Barr Laboratories, Inc. (KOS III) has been designated Civil Action No.: 02-CV-8995. KOS commenced the first related action KOS Pharmaceuticals vs. Barr Laboratories, Inc. (KOS I) in the U.S. District Court, Southern District of New York on March 7, 2001 and amended on March 11, 2002 (02-CV-1683). KOS commenced a second related action KOS Pharmaceuticals vs. Barr Laboratories, Inc. (KOS II) on August 13, 2002 (02-CV-6409) for the 500 mg and 750 mg strengths (ANDA 76-378). On September 23, 2002, Judge Marrero issued an Order consolidating KOS II with KOS I.

If you have any questions concerning this patent amendment, please contact me by phone at (845) 348-8051 or by fax at (845) 353-3859.

Sincerely,

BARR LABORATORIES, INC.

Nicholas Tantillo
Senior Director of Regulatory affairs

APPEARS THIS WAY
ON ORIGINAL

Barr Laboratories, Inc.

2 Quaker Road • P.O. Box 2900 • Pomona, NY 10970-0519 • 845/362-1100

December 13, 2002

ORIG AMENDMENT

N/Am

BIOAVAILABILITY

Office of Generic Drugs
Center for Drug Evaluation and Research
FOOD AND DRUG ADMINISTRATION
Document Control Room 150
Metro Park North II
7500 Standish Place
Rockville, Maryland 20855-2773

MINOR AMENDMENT

REFERENCE: **ANDA 76-250**
Niacin Extended Release Tablets, 1000 mg

Reference is made to our Abbreviated New Drug Application submitted on October 2, 2001 under Section 505(j) of the Federal Food, Drug and Cosmetic Act for Niacin Extended Release Tablets, 1000 mg.

Reference is also made to the October 7, 2002 minor deficiency (copy enclosed) containing chemistry comments. The Agency indicated that Barr's response would be considered a MINOR AMENDMENT.

Barr's responses to the Agency comments follows:

Chemistry Comments:

A. Deficiencies:

1. Please provide your current version of drug product release and stability specification, and a blank COA copy. Please acknowledge that the following dissolution testing has been incorporated into your manufacturing controls and stability program:

The dissolution testing should be conducted in 900 mL of water at 37° C using USP apparatus I (basket) at 100 rpm. The test products should meet the following interim specifications:

Time (Hours)	Amount Dissolved (%)
1	Not More Than —%
3	Between ———%
6	Between ———%
9	Between —— %
12	Between ———%
20	Not Less Than —%

Response:

Barr confirms that the Agency's recommended method has been incorporated in Barr's test method and all dissolution testing are being performed in 900 mL of water at 37° C using USP apparatus I (basket) at 100 rpm.

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Please note that Barr would like to propose the following specifications that differ from what the Agency is recommending for time points 3, 6, 9 and 12 hours.

Time (Hours)	Amount Dissolved (%)
1	Not More Than
3	Between
6	Between
9	Between
12	Between
20	Not Less Than

Barr's specifications are based on the mean drug release values obtained with the bio-batch that are provided below.

Time (Hours)	Range of Mean Drug Release obtained with the Biobatch		
	Initial Profile	21 month 100s	21 month 250s
1	11%	11%	9%
3	25%	24%	22%
6	42%	41%	37%
9	56%	54%	51%
12	68%	66%	64%
20	104%	102%	98%

According to the Guidance for Industry, Extended Release Oral Dosage Forms: Development, Evolution, and Application of In Vitro/In Vivo Correlation, "The recommended range at any dissolution time point specification is ± 10% deviation from the mean dissolution profile obtained from the clinical/bioavailability lots. In certain cases, reasonable deviations from ± 10% range can be accepted provided that the range at any time point does not exceed 25%." Based on the guidance and the data obtained with the bio-batch, the proposed specifications are justified for Niacin Extended Release Tablets, 1000 mg.

Barr has updated the Finished Product Specification Sheets and Test Method for Niacin Extended Release Tablets, 1000 mg to incorporate the above specifications for dissolution testing. Please find the updated specification sheets and test methods for Niacin Extended Release Tablets, 1000 mg in **Attachment I**.

Please note that the stability study results containing dissolution data for Niacin Extended Release Tablets, 1000 mg, Batch 202141002R, generated through three months of storage under accelerated testing conditions (40°C & 75%RH), and twenty-one months of storage under long term testing conditions (25°C & 60% RH) in the proposed marketing container/closure configurations are discussed in Stability Report, ARD-RTP-168. The stability study results for Niacin Extended Release Tablets, 1000 mg, Batch 202141002R, generated through twelve months of storage under long term conditions (25° C & 60% RH) in the bulk packaging configuration are discussed in ARD-RPT-177. Please find Stability Reports, ARD-RTP-168 and ARD-RPT-177 in **Attachment II**.

2. [redacted]

Response:

Please note that on November 25, 2002 Barr representatives had a teleconference with Dr. Paul Schwartz and Dr. Vilayat Sayeed of the Chemistry Divisions of the Office of Generic Drugs regarding in-process specifications. During the conference call, it was agreed that Barr would eliminate the [redacted]

3. **Please provide additional long term stability data that are available. The dissolution testing should include data for sampling time at 1, 3, 6, 9, 12, and 20 hours. You may also provide dissolution test results from the third month accelerated stability samples (if samples are still available) to support your proposed expiration dating period.**

Response:

The stability study results for Niacin Extended Release Tablets, 1000 mg, Batch: 202141002R, generated through three months of storage under accelerated testing conditions (40°C & 75%RH), and twenty-one months of storage under long term testing conditions (25°C & 60% RH) in the proposed marketing container/closure configurations are provided in Stability Report, ARD-RTP-168.

The stability study results for Niacin Extended Release Tablets, 1000 mg, Batch: 20141002R, generated through twelve months of storage under long term conditions (25° C & 60% RH) in the bulk packaging configuration are discussed in ARD-RPT-177.

Please find Stability Reports, ARD-RTP-168 and ARD-RPT-177 in **Attachment II**.

Please note that retained samples from the accelerated stability program were not available. Since there were no changes in the test method except for the specifications, the accelerated data submitted in the ANDA supports the proposed expiration dating of 24 months.

Barr has updated the Finished Product Specification Sheets and Test Method for Niacin Extended Release Tablets, 1000 mg to incorporate the above specifications for dissolution testing. Please find the updated specification sheets and test methods for Niacin Extended Release Tablets, 1000 mg in **Attachment I**.

Identical copies of this Amendment have been provided to the New York and Baltimore District Offices. A document certification is attached.

This completes the Minor Amendment. If you have any questions, please contact me by phone at (845) 348-8051 or by fax at (845) 353-3859.

Sincerely,

BARR LABORATORIES, INC.

Nicholas Tantillo
Senior Director of Regulatories Affairs

APPEARS THIS WAY
ON ORIGINAL

Barr Laboratories, Inc.

2 Quaker Road • P.O. Box 2900 • Pomona, NY 10970-0519 • 845/362-1100

February 24, 2003

ORIG AMENDMENT

N/AM

Office of Generic Drugs
Center for Drug Evaluation and Research
FOOD AND DRUG ADMINISTRATION
Document Control Room 150
Metro Park North II
7500 Standish Place
Rockville, Maryland 20855-2773

REFERENCE: **ANDA 76-250**
Niacin Extended Release Tablets, 1000 mg
TELEPHONE AMENDMENT

Reference is made to our Abbreviated New Drug Application submitted on October 2, 2001 under Section 505(j) of the Federal Food, Drug and Cosmetic Act for Niacin Extended Release Tablets, 1000 mg.

Reference is also made to the February 5, 2003 teleconference held with the Office of Generic Drugs and Barr representatives. The Agency indicated that Barr's response would be considered a TELEPHONE AMENDMENT.

Barr's response to the Agency comment follows:

Chemistry Comment:

> **Please provide 24 month stability data to support the expiration period of 24 month since drug release time points were revised. This revision was made due to earlier request by the Division of Bioequivalence.**
>
> **Response:**
>
> As requested by the Agency, 24 month stability data is provided to support our expiration period of 24 month for Niacin Extended Release Tablets, 1000 mg.

Identical copies of this amendment have been provided to the New York and Baltimore District Offices. A document certification is attached.

This completes the Telephone Amendment. If you have any questions, please contact me by phone at (845) 348-8051 or by fax at (845) 353-3859.

Sincerely,

BARR LABORATORIES, INC.

Nicholas Tantillo
Senior Director of Regulatories Affairs

RECEIVED
FEB 25 2003
OGD / CDER

2/25/03

Barr Laboratories, Inc.

2 Quaker Road • P.O. Box 2900 • Pomona, NY 10970-0519 • 845/362-1100

July 3, 2003

Office of Generic Drugs
Center for Drug Evaluation and Research
FOOD AND DRUG ADMINISTRATION
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, Maryland 20855-2773

NEW CORRESP
NC

76-250

GLOBAL CORRESPONDENCE
NEW TELEPHONE AND FACSIMILE CONTACT INFORMATION

REFERENCE: **See Attached List of pending and approved ANDAs**

This is to inform the Office of Generic Drugs that Barr Laboratories, Inc., and Duramed Pharmaceuticals, Inc., a subsidiary of Barr Laboratories, Inc., have the following new telephone numbers and facsimile number:

The Applicant's new telephone number is (201) 930-3300, and the new facsimile number is (201) 930-3318.

The Responsible Official's new telephone number is: 201-930-3650.

These new numbers will be in operation beginning on Thursday, July 3, 2003.

A signed and completed application form (356h) for each ANDA is attached.

Sincerely,

BARR LABORATORIES, INC.

William Tantillo (for)

Nicholas Tantillo
Senior Director,
Regulatory Affairs

cc: Gregory Davis, Deputy Director
DLPS, HFD 611
(Letter and attached list only)

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JUL 07 2003
OGD/CDER

NAI patent '967 listed in dockets
2/11/04 S. Middleton 2/24/04

January 15, 2004

Office of Generic Drugs
Center for Drug Evaluation and Research
FOOD AND DRUG ADMINISTRATION
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, Maryland 20855-2773

PATENT AMENDMENT NEW CORRESP
XP

REFERENCE: **ANDA 76-250**
NIACIN EXTENDED RELEASE TABLETS, 1000 MG

Reference is made to our Abbreviated New Drug Application dated October 2, 2001, submitted under Section 505(j) of the Federal Food and Cosmetic Act by Barr Laboratories, Inc. for Niacin Extended Release Tablets, 1000 mg.

In supplement to the above-referenced pending ANDA, this amendment contains a Paragraph IV Patent Certification for U.S. Patent No. 6676967.

Barr Laboratories will give the required notice under 21 CFR 314.95(a) to KOS Pharmaceuticals Inc., the NDA holder and the owner of U.S. Patent No. 6676967.

If you have any questions concerning this application, please contact me by phone at (201) 930-3650 or by fax at (201) 930-3318.

Sincerely,
BARR LABORATORIES, INC.

Nicholas Tantillo

Nicholas Tantillo
Senior Director Regulatory Affairs

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JAN 15 2004
OGD/CDER

NAI patent '967 listed in dockets 2/11/04 S. Middleton 2/24/04

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January 16, 2004

Office of Generic Drugs
Center for Drug Evaluation and Research
FOOD AND DRUG ADMINISTRATION
Document Control Room
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7500 Standish Place, Room 150
Rockville, Maryland 20855-2773

PATENT AMENDMENT

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Sincerely,
BARR LABORATORIES, INC.

Nicholas Tantillo FJC
Nicholas Tantillo
Senior Director Regulatory Affairs

NAI patent '967 listed in dockets
2/11/04 S. Middleton 2/24/04

XP

January 21, 2004

Office of Generic Drugs
Center for Drug Evaluation and Research
FOOD AND DRUG ADMINISTRATION
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, Maryland 20855-2773

PATENT AMENDMENT

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Sincerely,
BARR LABORATORIES, INC.

Nicholas Tantillo
Senior Director Regulatory Affairs

Barr Laboratories, Inc.

NAI patent 1967 not listed in OB or dockets S. Middleton 2/1/04

Suite 722, 444 North Capitol Street, NW, Washington, DC 20001 • 202/393-6599, Fax 202/638-3386

January 21, 2004

Office of Generic Drugs
Center for Drug Evaluation and Research
FOOD AND DRUG ADMINISTRATION
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, Maryland 20855-2773

N/xp

PATENT AMENDMENT

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Sincerely,
BARR LABORATORIES, INC.

Nicholas Tantillo (fa)

Nicholas Tantillo
Senior Director Regulatory Affairs

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JAN 26 2004
OGD/CDER

NAI patent '967 listed in dockets
2/11/04 S. Middleton 2/24/04

Barr Laboratories, Inc.

Suite 722, 444 North Capitol Street, NW, Washington, DC 20001 - 202/393-6599, Fax 202/638-3386

January 22, 2004

Office of Generic Drugs
Center for Drug Evaluation and Research
FOOD AND DRUG ADMINISTRATION
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, Maryland 20855-2773

XP

PATENT AMENDMENT

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Sincerely,
BARR LABORATORIES, INC.

Nicholas Tantillo (ee)
Nicholas Tantillo
Senior Director, Regulatory Affairs

RECEIVED
JAN 22 2004
OGD/CDER

NAI patent '967 listed in dockets 2/11/04 S. Middleton 2/24/04

Barr Laboratories, Inc.

400 Chestnut Ridge Rd., Woodcliff Lake, NJ 07677-7668

January 23, 2004

Office of Generic Drugs
Center for Drug Evaluation and Research
FOOD AND DRUG ADMINISTRATION
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, Maryland 20855-2773

XP

PATENT AMENDMENT

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Sincerely,
BARR LABORATORIES, INC.

Nicholas Tantillo (gdl)
Nicholas Tantillo
Senior Director, Regulatory Affairs

NAI patent '967 listed in dockets
2/11/04 S. Middleton 2/24/04

Barr Laboratories, Inc.

400 Chestnut Ridge Road, Woodcliff Lake, NJ 07677-7668

January 27, 2004

XP

Office of Generic Drugs
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Sincerely,
BARR LABORATORIES, INC.

Nicholas Tantillo FJK
Nicholas Tantillo
Senior Director, Regulatory Affairs

RECEIVED
JAN 28 2004
OGD/CDER

Barr Laboratories, Inc.

NAI patent 6967 not listed in OB or dockets S. Middleton 2/1/04

400 Chestnut Ridge Road, Woodcliff Lake, NJ 07677-7668

January 28, 2004

Office of Generic Drugs
Center for Drug Evaluation and Research
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Rockville, Maryland 20855-2773

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Sincerely,
BARR LABORATORIES, INC.

Nicholas Tantillo (3dl)

Nicholas Tantillo
Senior Director, Regulatory Affairs

RECEIVED
JAN 28 2004
OGD/ODER

Barr Laboratories, Inc.

400 Chestnut Ridge

NAI patent '967 listed in dockets
2/11/04 S. Middleton 2/24/04

January 29, 2004

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Center for Drug Evaluation and Research
FOOD AND DRUG ADMINISTRATION
Document Control Room
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Rockville, Maryland 20855-2773

PATENT AMENDMENT XP

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Sincerely,
BARR LABORATORIES, INC.

Nicholas Tantillo
Senior Director, Regulatory Affairs

Barr Laboratories, Inc.

Suite 722, 444 North Capitol Street, NW, Washington, DC 20001

NAI patent '967 listed in dockets 2/11/04 S. Middleton 2/24/04

January 30, 2004

ORIG AMENDMENT
X P

Office of Generic Drugs
Center for Drug Evaluation and Research
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Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, Maryland 20855-2773

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Sincerely,
BARR LABORATORIES, INC.

Nicholas Tantillo (fax)

Nicholas Tantillo
Senior Director, Regulatory Affairs

RECEIVED
JAN 30 2004
OGD/CDER

Barr Laboratories, Inc.

Suite 722, 444 North Capitol Street, NW, Washington, DC 20

NAI patent '967 listed in dockets 2/11/04 S. Middleton 2/24/04

February 2, 2004

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Office of Generic Drugs
Center for Drug Evaluation and Research
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Sincerely,
BARR LABORATORIES, INC.

Nicholas Tantillo (sa)
Nicholas Tantillo
Senior Director, Regulatory Affairs

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OGD/CDER

Barr Laboratories, Inc.

Suite 722, 444 North Capitol Street, NW, Washington, DC 20001 •

NAI patent '967 listed in dockets
2/11/04 S. Middleton 2/24/04

February 3, 2004

ORIG AMENDMENT
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Office of Generic Drugs
Center for Drug Evaluation and Research
FOOD AND DRUG ADMINISTRATION
Document Control Room
Metro Park North II
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Nicholas Tantillo (sa)
Nicholas Tantillo
Senior Director, Regulatory Affairs

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FEB 0 3 2004
OGD/CDER

Barr Laboratories, Inc.

NAI patent '967 listed in dockets 2/11/04 S. Middleton 2/24/04

Suite 722, 444 North Capitol Street, NW, Washington, DC 200 ..-6599, Fax 202/638-3386

February 4, 2004

XP

Office of Generic Drugs
Center for Drug Evaluation and Research
FOOD AND DRUG ADMINISTRATION
Document Control Room
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Rockville, Maryland 20855-2773

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Sincerely,
BARR LABORATORIES, INC.

Nicholas Tantillo (sa)

Nicholas Tantillo
Senior Director, Regulatory Affairs

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FEB 0 4 2004
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Barr Laboratories, Inc.

Suite 722, 444 North Capitol Street, NW, Washington, DC ... 2027 638-3386

NAI patent '967 listed in dockets 2/11/04 S. Middleton 2/24/04

February 5, 2004

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Office of Generic Drugs
Center for Drug Evaluation and Research
FOOD AND DRUG ADMINISTRATION
Document Control Room
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Rockville, Maryland 20855-2773

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Sincerely,
BARR LABORATORIES, INC.

Nicholas Tantillo (fa)
Nicholas Tantillo
Senior Director, Regulatory Affairs

RECEIVED
FEB 05 2004
OGD/CDER

Barr Laboratories, Inc.

Suite 722, 444 North Capitol Street, NW, Washington, DC 200

NAI patent '967 listed in dockets
2/11/04 S. Middleton 2/24/04

February 6, 2004

ORIG AMENDMENT
X P

Office of Generic Drugs
Center for Drug Evaluation and Research
FOOD AND DRUG ADMINISTRATION
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Rockville, Maryland 20855-2773

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Sincerely,
BARR LABORATORIES, INC.

Nicholas Tantillo (ea)
Nicholas Tantillo
Senior Director, Regulatory Affairs

RECEIVED
FEB 0 6 2004
OGD/CDER

Barr Laboratories, Inc.

Suite 722, 444 North Capitol Street, NW, Washington, DC 20

NAI patent '967 listed in dockets 2/11/04 S. Middleton 2/24/04

XP

February 9, 2004

Office of Generic Drugs
Center for Drug Evaluation and Research
FOOD AND DRUG ADMINISTRATION
Document Control Room
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Rockville, Maryland 20855-2773

PATENT AMENDMENT

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Sincerely,
BARR LABORATORIES, INC.

Nicholas Tantillo (sa)

Nicholas Tantillo
Senior Director, Regulatory Affairs

Barr Laboratories, Inc.

Suite 722, 444 North Capitol Street, NW, Washington, DC

NAI patent '967 listed in dockets 2/11/04 S. Middleton 2/24/04

February 10, 2004

Office of Generic Drugs
Center for Drug Evaluation and Research
FOOD AND DRUG ADMINISTRATION
Document Control Room
Metro Park North II
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Rockville, Maryland 20855-2773

XP

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Sincerely,
BARR LABORATORIES, INC.

Nicholas Tantillo (sa)
Nicholas Tantillo
Senior Director, Regulatory Affairs

RECEIVED
FEB 10 2004

Barr Laboratories, Inc.

NAI patent '967 listed in dockets 2/11/04 S. Middleton 2/24/04

Suite 722, 444 North Capitol Street, NW, Washington, D[illegible], Fax 202/638-3386

February 11, 2004

Office of Generic Drugs
Center for Drug Evaluation and Research
FOOD AND DRUG ADMINISTRATION
Document Control Room
Metro Park North II
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N/xp

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Sincerely,
BARR LABORATORIES, INC.

Nicholas Tantillo (for)
Nicholas Tantillo
Senior Director, Regulatory Affairs

RECEIVED
FEB 11 2004
OGD/CDER

Barr Laboratories, Inc.

Suite 722, 444 North Capitol Street, NW, Washington, DC 20001 •

NAI patent '967 listed in dockets 2/11/04 S. Middleton 2/24/04

February 12, 2004

ORIG AMENDMENT
x9

Office of Generic Drugs
Center for Drug Evaluation and Research
FOOD AND DRUG ADMINISTRATION
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, Maryland 20855-2773

PATENT AMENDMENT

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Sincerely,
BARR LABORATORIES, INC.

Nicholas Tantillo (FAX)
Nicholas Tantillo
Senior Director, Regulatory Affairs

RECEIVED
FEB 12 2004
OGD / CDER

Barr Laboratories, Inc.

Suite 722, 444 North Capitol Street, NW, Washington, DC 20

NAI patent '967 listed in dockets 2/11/04 S. Middleton 2/24/04

February 13, 2004

Office of Generic Drugs
Center for Drug Evaluation and Research
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Nicholas Tantillo (CC)

Nicholas Tantillo
Senior Director, Regulatory Affairs

Barr Laboratories, Inc.

NAI patent '967 listed in dockets 2/11/04 S. Middleton 2/24/04

Suite 722, 444 North Capitol Street, NW, Washington, DC 20001

February 17, 2004

N/xp

Office of Generic Drugs
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Sincerely,
BARR LABORATORIES, INC.

Nicholas Tantillo
Senior Director, Regulatory Affairs

RECEIVED
FEB 17 2004
OGD / CDER

Barr Laboratories, Inc.

Suite 722, 444 North Capitol Street, NW, Washington, DC 20001 • 202/3[illegible]

NAI patent '967 listed in dockets
2/11/04 S. Middleton 2/24/04

February 18, 2004

XP

Office of Generic Drugs
Center for Drug Evaluation and Research
FOOD AND DRUG ADMINISTRATION
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, Maryland 20855-2773

PATENT AMENDMENT

REFERENCE: **ANDA 76-250**
NIACIN EXTENDED RELEASE TABLETS, 1000 MG

Reference is made to our Abbreviated New Drug Application dated October 2, 2001, submitted under Section 505(j) of the Federal Food and Cosmetic Act by Barr Laboratories, Inc. for Niacin Extended Release Tablets, 1000 mg.

In supplement to the above-referenced pending ANDA, this amendment contains a Paragraph IV Patent Certification for U.S. Patent No. 6676967.

Barr Laboratories will give the required notice under 21 CFR 314.95(a) to KOS Pharmaceuticals Inc., the NDA holder and the owner of U.S. Patent No. 6676967.

If you have any questions concerning this application, please contact me by phone at (201) 930-3650 or by fax at (201) 930-3318.

Sincerely,
BARR LABORATORIES, INC.

Nicholas Tantillo (ap)

Nicholas Tantillo
Senior Director, Regulatory Affairs

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FEB 18 2004
OGD/CDER

NAI patent '967 listed in dockets
2/11/04 S. Middleton 2/24/04

Barr Laboratories, Inc.

Suite 722, 444 North Capitol Street, NW, Washington, DC 20001 • 202/393-6599, Fax 202/638-3386

February 19, 2004

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Office of Generic Drugs
Center for Drug Evaluation and Research
FOOD AND DRUG ADMINISTRATION
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, Maryland 20855-2773

PATENT AMENDMENT

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If you have any questions concerning this application, please contact me by phone at (201) 930-3650 or by fax at (201) 930-3318.

Sincerely,
BARR LABORATORIES, INC.

Nicholas Tantillo

Nicholas Tantillo
Senior Director, Regulatory Affairs

Barr Laboratories, Inc.

Suite 722, 444 North Capitol Street, NW, Washington, DC 20

NAI patent '967 listed in dockets 2/11/04 S. Middleton 2/24/04

February 20, 2004

Office of Generic Drugs
Center for Drug Evaluation and Research
FOOD AND DRUG ADMINISTRATION
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Metro Park North II
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PATENT AMENDMENT

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Sincerely,
BARR LABORATORIES, INC.

Nicholas Tantillo (gdl)

Nicholas Tantillo
Senior Director, Regulatory Affairs

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FEB 20 2004
OGD/CDER

"PR Saved within 45 days S. Middleton 7/12/04

Barr Laboratories, Inc.

2 Quaker Road • P.O. Box 2900 • Pomona, NY 10970-0519 • 845/362-1100

April 2, 2004

XP

Office of Generic Drugs
Center for Drug Evaluation and Research
FOOD AND DRUG ADMINISTRATION
Document Control Room 150
Metro Park North II
7500 Standish Place
Rockville, Maryland 20855-2773

PATENT AMENDMENT

REFERENCE: ANDA 76-250
NIACIN EXTENDED RELEASE TABLETS, 1000 MG

Reference is made to our Abbreviated New Drug Application dated October 2, 2001, submitted under Section 505(j) of the Federal Food and Cosmetic Act by Barr Laboratories, Inc. for Niacin Extended Release Tablets, 1000 mg.

In accordance with our Patent Certification Statement submitted on February 20, 2004 under 21 CFR §314.95(a) and (d), notice was sent by certified mail on February 20, 2004 return receipt requested to the owner of U.S. Patent No. 6,679,967 which is the subject of the certification and to the holder of the approved application under Section 505(b) of the Act.

In accordance with 21 CFR §314.95(d), Barr is hereby submitting a Patent Amendment to certify that notice was provided to KOS Pharmaceuticals, Inc. (Owner of the patent and NDA holder) by Sterne, Kessler, Goldstein and Fox P.L.L.C on behalf of Barr Laboratories Inc.

The contents of the notice letter comply with 21 CFR §314.95(c). The notice letter cites the appropriate section of the Act. In this notice letter, Barr alleges that in its opinion U.S. Patent No. 6,679,967 is invalid, unenforceable or will not be infringed by the manufacture, use, or sale of Barr's Niacin Extended Release Tablets, 1000 mg.

In accordance with 21 CFR §314.95(e), enclosed please find a copy of the return receipt from KOS Pharmaceuticals, Inc. for the notice, which was delivered on February 24, 2004.

Barr is hereby submitting a Patent Amendment to certify that Barr Laboratories, Inc. has received notice of litigation from KOS Pharmaceuticals, Inc. within the 45-day period as provided for in section 505 (j)(4)(B)(iii) of the Act. The case, KOS Pharmaceuticals, Inc. vs. Barr Laboratories, Inc., Civil Action No.: 04CV2403 in the U.S. District Court, Southern District of New York was filed on March 26, 2004. Further, Barr agrees to submit a copy of the court order or judgment or settlement agreement between Barr and KOS Pharmaceuticals or a licensing agreement between Barr and the patent holder or any other relevant information.

If you have any questions concerning this patent amendment, please contact me by phone at (201) 930-3650 or by fax at (201) 930-3318.

Sincerely,
BARR LABORATORIES, INC.

Nicholas Tantillo
Senior Director, Regulatory Affairs

ORIGINAL

Barr Laboratories, Inc.

2 Quaker Road • P.O. Box 2900 • Pomona, NY 10970-0519 • 845/362-1100

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27 May 2004
change
patent #
XP

May 26, 2003

Office of Generic Drugs
Center for Drug Evaluation and Research
FOOD AND DRUG ADMINISTRATION
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, Maryland 20855-2773

PATENT AMENDMENT

<u>REFERENCE:</u> **ANDA 76-250**
NIACIN EXTENDED RELEASE TABLETS, 1000 MG

Reference is made to our Pending Abbreviated New Drug Application submitted under Section 505(j) of the Federal Food, Drug and Cosmetic Act for Niacin Extended Release Tablets, 1000 mg submitted on October 2, 2001.

This submission is in reference to our Patent Amendment submitted on April 2, 2004, where Barr inadvertently referenced the U.S. Patent No. as 6,679,967. The correct U.S. Patent No. 6,676,967, was accurately stated in our patent amendment dated February 20, 2004 and our notice to KOS Pharmaceuticals, Inc. This amendment is being submitted to inform the Agency that the U.S Patent No. 6,679,967 that was submitted in the April 2, 2004 patent amendment is incorrect and that U.S. Patent No. 6,676,967 is the correct patent number.

If you have any questions concerning this application, please contact me by phone at (201) 930-3650 or by fax at (201) 930-3650.

Sincerely,
BARR LABORATORIES, INC.

Nicholas Tantillo
Senior Director, Regulatory Affairs

RECEIVED
MAY 27 2004
OGD/CDER

Barr Laboratories, Inc.

Suite 722, 444 North Capitol Street, NW, Washington, DC 20001 • 202/393-6599, Fax 202/638-3386

June 8, 2004

Office of Generic Drugs
Center for Drug Evaluation and Research
FOOD AND DRUG ADMINISTRATION
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, Maryland 20855-2773

XP

PATENT AMENDMENT

REFERENCE: **ANDA 76-250**
NIACIN EXTENDED RELEASE TABLETS, 1000 MG

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In supplement to the above-referenced pending ANDA, this amendment contains a Paragraph IV Patent Certification for U.S. Patent No. 6746691B2.

Barr Laboratories will give the required notice under 21 CFR 314.95(a) to KOS Pharmaceuticals Inc., the NDA holder and the owner of U.S. Patent No. 6746691B2.

If you have any questions concerning this application, please contact me by phone at (201) 930-3650 or by fax at (201) 930-3318.

Sincerely,
BARR LABORATORIES, INC.

Nicholas Tantillo
Senior Director Regulatory Affairs

Barr Laboratories, Inc.

Suite 722, 444 North Capitol Street, NW, Washington, DC 20001 • 202/393-6599, Fax 202/638-3386

XP

June 9, 2004

Office of Generic Drugs
Center for Drug Evaluation and Research
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Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, Maryland 20855-2773

ORIGINAL

NAI patent '691 not listed in OB or dockets C. Bina

JUL 14 2004

PATENT AMENDMENT

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If you have any questions concerning this application, please contact me by phone at (201) 930-3650 or by fax at (201) 930-3318.

Sincerely,
BARR LABORATORIES, INC.

Nicholas Tantillo (LA)

Nicholas Tantillo
Senior Director Regulatory Affairs

RECEIVED
JUN 09 2004
OGD/CDER

Barr Laboratories, Inc.

Suite 722, 444 North Capitol Street, NW, Washington, DC 20001 • 202/393-6599, Fax 202/638-3386

June 10, 2004

Office of Generic Drugs
Center for Drug Evaluation and Research
FOOD AND DRUG ADMINISTRATION
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N/KP

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Sincerely,
BARR LABORATORIES, INC.

Nicholas Tantillo (fax)

Nicholas Tantillo
Senior Director Regulatory Affairs

ORIGINAL

Barr Laboratories, Inc.

Suite 722, 444 North Capitol Street, NW, Washington, DC 20001 • 202/393-6599, Fax 202/638-3386

June 14, 2004

XP

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NAI patent '691 not listed in OB or dockets C. Bina
JUL 14 2004

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Sincerely,
BARR LABORATORIES, INC.

Nicholas Tantillo (fax)

Nicholas Tantillo
Senior Director Regulatory Affairs

RECEIVED
JUN 14 2004
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Barr Laboratories, Inc.

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June 15, 2004

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Center for Drug Evaluation and Research
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Sincerely,
BARR LABORATORIES, INC.

Nicholas Tantillo (fax)

Nicholas Tantillo
Senior Director Regulatory Affairs

RECEIVED
JUN 15 2004
OGD/GDAR

XP

Barr Laboratories, Inc.

Suite 722, 444 North Capitol Street, NW, Washington, DC 20001 • 202/393-6599, Fax 202/638-3386

June 16, 2004

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Metro Park North II
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Rockville, Maryland 20855-2773

ORIGINAL

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Sincerely,
BARR LABORATORIES, INC.

Nicholas Tantillo (FAX)

Nicholas Tantillo
Senior Director Regulatory Affairs

RECEIVED
JUN 16 2004
OGD/DOER

Barr Laboratories, Inc.

Suite 722, 444 North Capitol Street, NW, Washington, DC 20001 • 202/393-6599, Fax 202/638-3386

June 17, 2004

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Center for Drug Evaluation and Research
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7500 Standish Place, Room 150
Rockville, Maryland 20855-2773

NAI patent 6691 not listed in OB or dockets C. Bina

JUL 14 2004

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Sincerely,
BARR LABORATORIES, INC.

Nicholas Tantillo (for)
Nicholas Tantillo
Senior Director Regulatory Affairs

RECEIVED
JUN 17 2004

ORIGINAL

Barr Laboratories, Inc.

Suite 722, 444 North Capitol Street, NW, Washington, DC 20001 • 202/393-6599, Fax 202/638-3386

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June 18, 2004

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Sincerely,
BARR LABORATORIES, INC.

Nicholas Tantillo (fax)

Nicholas Tantillo
Senior Director Regulatory Affairs

RECEIVED
JUN 18 2004
OGD/CDER

Barr Laboratories, Inc.

Suite 722, 444 North Capitol Street, NW, Washington, DC 20001 • 202/393-6599, Fax 202/638-3386

June 21, 2004

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NAI patent '691 not listed in OB or dockets C. Bina

JUL 14 2004

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Sincerely,
BARR LABORATORIES, INC.

Nicholas Tantillo (fax)

Nicholas Tantillo
Senior Director Regulatory Affairs

RECEIVED
JUN 21 2004
OGD / CDER

Barr Laboratories, Inc.

Suite 722, 444 North Capitol Street, NW, Washington, DC 20001 • 202/393-6599, Fax 202/638-3386

June 22, 2004

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PATENT AMENDMENT

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Sincerely,
BARR LABORATORIES, INC.

Nicholas Tantillo (FR)

Nicholas Tantillo
Senior Director Regulatory Affairs

RECEIVED
JUN 22 2004
OGD / CDER

ORIGINAL

Barr Laboratories, Inc.

Suite 722, 444 North Capitol Street, NW, Washington, DC 20001 • 202/393-6599, Fax 202/638-3386

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JUL 14 2004

June 23, 2004

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Sincerely,
BARR LABORATORIES, INC.

Nicholas Tantillo (fa)

Nicholas Tantillo
Senior Director Regulatory Affairs

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JUN 23 2004
OGD/CDER

ORIGINAL

Barr Laboratories, Inc.

Suite 722, 444 North Capitol Street, NW, Washington, DC 20001 • 202/393-6599, Fax 202/638-3386

June 24, 2004

NAI patent (69) not listed in OB or dockets C. Bina
JUL 14 2004

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Sincerely,
BARR LABORATORIES, INC.

Nicholas Tantillo (fa)

Nicholas Tantillo
Senior Director, Regulatory Affairs

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JUN 24 2004
OGD / CDER

RECEIVED
JUN 25 2004
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ORIGINAL

Barr Laboratories, Inc.

Suite 722, 444 North Capitol Street, NW, Washington, DC 20001 • 202/393-6599, Fax 202/638-3386

June 25, 2004

NAI patent 6691 not listed in OB or dockets C. Bina
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Sincerely,
BARR LABORATORIES, INC.

Nicholas Tantillo (by)

Nicholas Tantillo
Senior Director, Regulatory Affairs

RECEIVED
JUN 25 2004
OGD / CDER

Barr Laboratories, Inc.

ORIGINAL

Suite 722, 444 North Capitol Street, NW, Washington, DC 20001 • 202/393-6599, Fax 202/638-3386

June 28, 2004

Office of Generic Drugs
Center for Drug Evaluation and Research
FOOD AND DRUG ADMINISTRATION
Document Control Room
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7500 Standish Place, Room 150
Rockville, Maryland 20855-2773

NAI patent 6691 not listed in OB or dockets C. Bina
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Sincerely,
BARR LABORATORIES, INC.

Nicholas Tantillo (for)

Nicholas Tantillo
Senior Director, Regulatory Affairs

RECEIVED
JUN 28 2004
OGD / CDER

ORIGINAL

Barr Laboratories, Inc.

Suite 722, 444 North Capitol Street, NW, Washington, DC 20001 • 202/393-6599, Fax 202/638-3386

June 29, 2004

NAI patent 6691 not listed in OB or dockets C. Bina

JUL 14 2004

XP

Office of Generic Drugs
Center for Drug Evaluation and Research
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PATENT AMENDMENT

REFERENCE: **ANDA 76-250**
NIACIN EXTENDED RELEASE TABLETS, 1000 MG

Reference is made to our Abbreviated New Drug Application dated October 2, 2001, submitted under Section 505(j) of the Federal Food and Cosmetic Act by Barr Laboratories, Inc. for Niacin Extended Release Tablets, 1000 mg.

In supplement to the above-referenced pending ANDA, this amendment contains a Paragraph IV Patent Certification for U.S. Patent No. 6746691B2.

Barr Laboratories will give the required notice under 21 CFR 314.95(a) to KOS Pharmaceuticals Inc., the NDA holder and the owner of U.S. Patent No. 6746691B2.

If you have any questions concerning this application, please contact me by phone at (201) 930-3650 or by fax at (201) 930-3318.

Sincerely,
BARR LABORATORIES, INC.

Nicholas Tantillo (La)

Nicholas Tantillo
Senior Director, Regulatory Affairs

RECEIVED
JUN 29 2004
OGD / CDER

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JUN 29 2004
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Barr Laboratories, Inc.

ORIGINAL

3.1

Suite 722, 444 North Capitol Street, NW, Washington, DC 20001 • 202/393-6599, Fax 202/638-3386

June 30, 2004

Office of Generic Drugs
Center for Drug Evaluation and Research
FOOD AND DRUG ADMINISTRATION
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, Maryland 20855-2773

XP

NAI patent -691 not listed in OB or dockets C. Bina
JUL 14 2004

PATENT AMENDMENT

REFERENCE: **ANDA 76-250**
NIACIN EXTENDED RELEASE TABLETS, 1000 MG

Reference is made to our Abbreviated New Drug Application dated October 2, 2001, submitted under Section 505(j) of the Federal Food and Cosmetic Act by Barr Laboratories, Inc. for Niacin Extended Release Tablets, 1000 mg.

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Sincerely,
BARR LABORATORIES, INC.

Nicholas Tantillo (fax)

Nicholas Tantillo
Senior Director, Regulatory Affairs

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JUN 30 2004
OGD / CDER

3.1

Barr Laboratories, Inc. **ORIGINAL**

Suite 722, 444 North Capitol Street, NW, Washington, DC 20001 • 202/393-6599, Fax 202/638-3386

July 1, 2004

Office of Generic Drugs
Center for Drug Evaluation and Research
FOOD AND DRUG ADMINISTRATION
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, Maryland 20855-2773

XP

NAI patent '691 not listed in OB or dockets C. Bina
JUL 14 2004

PATENT AMENDMENT

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Sincerely,
BARR LABORATORIES, INC.

Nicholas Tantillo (HR)

Nicholas Tantillo
Senior Director, Regulatory Affairs

RECEIVED
JUL 01 2004
OGD / CDER

Barr Laboratories, Inc.

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3.1

Suite 722, 444 North Capitol Street, NW, Washington, DC 20001 • 202/393-6599, Fax 202/638-3386

July 2, 2004

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Center for Drug Evaluation and Research
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Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, Maryland 20855-2773

NAI patent 6691 not listed in OB or dockets C. Bina
JUL 14 2004

PATENT AMENDMENT

REFERENCE: **ANDA 76-250**
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Sincerely,
BARR LABORATORIES, INC.

Nicholas Tantillo (RA)

Nicholas Tantillo
Senior Director, Regulatory Affairs

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JUL 0 2 2004
OGD / CDER

ORIGINAL

Barr Laboratories, Inc.

Suite 722, 444 North Capitol Street, NW, Washington, DC 20001 • 202/393-6599, Fax 202/638-3386

July 6, 2004

NAI patent 6691 not listed in OB or dockets C. Bina 7/21/04

Office of Generic Drugs
Center for Drug Evaluation and Research
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Document Control Room
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7500 Standish Place, Room 150
Rockville, Maryland 20855-2773

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PATENT AMENDMENT

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Sincerely,
BARR LABORATORIES, INC.

Nicholas Tantillo (fa)

Nicholas Tantillo
Senior Director, Regulatory Affairs

RECEIVED
JUL 0 6 2004
OGD / CDER

Barr Laboratories, Inc.

Suite 722, 444 North Capitol Street, NW, Washington, DC 20001 • 202/393-6599, Fax 202/638-3386

July 7, 2004

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Office of Generic Drugs
Center for Drug Evaluation and Research
FOOD AND DRUG ADMINISTRATION
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, Maryland 20855-2773

NAI patent \ 69 not listed in OB or dockets C. Bina JUL 14 2004

PATENT AMENDMENT

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NIACIN EXTENDED RELEASE TABLETS, 1000 MG

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If you have any questions concerning this application, please contact me by phone at (201) 930-3650 or by fax at (201) 930-3318.

Sincerely,
BARR LABORATORIES, INC.

Nicholas Tantillo (fax)

Nicholas Tantillo
Senior Director, Regulatory Affairs

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JUL 0 7 2004
OGD / CDER

Barr Laboratories, Inc.

Suite 722, 444 North Capitol Street, NW, Washington, DC 20001 • 202/393-6599, Fax 202/638-3386

P/N Patent Cert to .691 to FDA (OK-SD 7/8/04)

July 8, 2004

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Center for Drug Evaluation and Research
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Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, Maryland 20855-2773

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7/29/04

PATENT AMENDMENT

REFERENCE: **ANDA 76-250**
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If you have any questions concerning this application, please contact me by phone at (201) 930-3650 or by fax at (201) 930-3318.

Sincerely,
BARR LABORATORIES, INC.

Nicholas Tantillo (fa)

Nicholas Tantillo
Senior Director, Regulatory Affairs

NAI
Letter that notice was
rec'd by KOS for '691
on 7/13/2004

Barr Laboratories, Inc.

2 Quaker Road • P.O. Box 2900 • Pomona, NY 10970-0519 • 845/362-1100

10/20/04

August 23, 2004

Office of Generic Drugs
Center for Drug Evaluation and Research
FOOD AND DRUG ADMINISTRATION
Document Control Room 150
Metro Park North II
7500 Standish Place
Rockville, Maryland 20855-2773

N/xp

PATENT AMENDMENT

REFERENCE: ANDA 76-250
NIACIN EXTENDED RELEASE TABLETS, 1000 MG

Reference is made to our Abbreviated New Drug Application dated October 2, 2001, submitted under Section 505(j) of the Federal Food and Cosmetic Act by Barr Laboratories, Inc. for Niacin Extended Release Tablets, 1000 mg.

Reference is also made to our July 8, 2004 patent amendment.

In accordance with the Patent Certification Statement submitted in our July 8, 2004, patent amendment under 21 CFR §314.95(a) and (d), notice was sent by certified mail on July 8, 2004 return receipt requested to the owner of U.S. Patent No. 6,746,691 B2 which is the subject of the certification and to the holder of the approved application under Section 505(b) of the Act.

In accordance with 21 CFR §314.95(d), Barr is hereby submitting this Patent Amendment to certify that notice was provided to KOS Pharmaceuticals, Inc. (Owner of the patent and NDA holder) by Sterne, Kessler, Goldstein and Fox P.L.L.C on behalf of Barr Laboratories Inc.

The contents of the notice letter comply with 21 CFR §314.95(c). The notice letter cites the appropriate section of the Act. In this notice letter, Barr alleges that in its opinion U.S. Patent No. 6,746,691 B2 is invalid, unenforceable or will not be infringed by the manufacture, use, or sale of Barr's Niacin Extended Release Tablets, 1000 mg.

In accordance with 21 CFR §314.95(e), enclosed please find a copy of the track and confirmation page from the United States Post Office website confirming that the item was accepted at the post office on July 08, 2004. Unfortunately, the post office has misplaced the return receipt for this item. Attached is a copy of the cover page of our notice sent by Sterne, Kessler, Goldstein, and Fox which references the tracking number.

Barr requested written confirmation from KOS that the notice sent on July 8, 2004 was received at KOS. A copy of the response from [redacted] on behalf of KOS is also enclosed, along with written notification from KOS that the notice was received on July 13, 2004.

If you have any questions concerning this patent amendment, please contact me by phone at (201) 930-3650 or by fax at (201) 930-3318.

Sincerely,
BARR LABORATORIES, INC.

Nicholas Tantillo
Senior Director, Regulatory Affairs

APPEARS THIS WAY
ON ORIGINAL

NA sued within 45 days for '691 B2 S. Middleton 10/25/04

Barr Laboratories, Inc.

2 Quaker Road • P.O. Box 2900 • Pomona, NY 10970-0519 • 845/362-1100

September 17, 2004

Office of Generic Drugs
Center for Drug Evaluation and Research
FOOD AND DRUG ADMINISTRATION
Document Control Room 150
Metro Park North II
7500 Standish Place
Rockville, Maryland 20855-2773

NKP

PATENT AMENDMENT

REFERENCE: ANDA 76-250
NIACIN EXTENDED RELEASE TABLETS, 1000 MG

Reference is made to our Abbreviated New Drug Application dated October 2, 2001, submitted under Section 505(j) of the Federal Food and Cosmetic Act by Barr Laboratories, Inc. for Niacin Extended Release Tablets, 1000 mg.

In accordance with our Patent Certification Statement submitted on August 23, 2004 under 21 CFR §314.95(a) and (d), notice was sent by certified mail on July 8, 2004 return receipt requested to the owner of U.S. Patent No. 6,746,691 B2 which is the subject of the certification and to the holder of the approved application under Section 505(b) of the Act.

Barr is hereby submitting a Patent Amendment to certify that the 45-day period, as provided for in section 505 (j)(4)(B)(iii) of the Act, to initiate litigation has expired. However, no complaints regarding U.S. Patent No. 6,746,691 B2 has been filed by KOS Pharmaceuticals, Inc. within the statutory period.

If you have any questions concerning this patent amendment, please contact me by phone at (201) 930-3650 or by fax at (201) 930-3318.

Sincerely,
BARR LABORATORIES, INC.

Nicholas Tantillo
Senior Director, Regulatory Affairs

Barr Laboratories, Inc.

Suite 722, 444 North Capitol Street, NW, Washington, DC 20001 • 202/393-6599, Fax 202/638-3386

November 16, 2004

Office of Generic Drugs
Center for Drug Evaluation and Research
FOOD AND DRUG ADMINISTRATION
Document Control Room 150
Metro Park North II
7500 Standish Place
Rockville, Maryland 20855-2773

XP

NAI patent 229 not listed in OB or dockets C. Bina
11/23/04

PATENT AMENDMENT

REFERENCE: ANDA 76-250
NIACIN EXTENDED RELEASE TABLETS, 1000 MG

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Barr Laboratories will give the required notice under 21 CFR 314.95(a) to KOS Pharmaceuticals Inc., the NDA holder and the owner of U.S. Patent No. 6818229.

If you have any questions concerning this application, please contact me by phone at (201) 930-3650 or by fax at (201) 930-3318.

Sincerely,
BARR LABORATORIES, INC.

Nicholas Tantillo (sa)

Nicholas Tantillo
Senior Director Regulatory Affairs

CDR stamp date not known
'229 patent listed in
OB 12/20/2004
per C. Bina 2/11/2005

Barr Laboratories, Inc.

Suite 722, 444 North Capitol Street, NW, Washington, DC 20001 • 202/393-6599, Fax 202/638-3386

November 17, 2004

Office of Generic Drugs
Center for Drug Evaluation and Research
FOOD AND DRUG ADMINISTRATION
Document Control Room 150
Metro Park North II
7500 Standish Place
Rockville, Maryland 20855-2773

N/xP

PATENT AMENDMENT

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If you have any questions concerning this application, please contact me by phone at (201) 930-3650 or by fax at (201) 930-3318.

Sincerely,
BARR LABORATORIES, INC.

Nicholas Tantillo (LA)

Nicholas Tantillo
Senior Director Regulatory Affairs

Barr Laboratories, Inc.

Suite 722, 444 North Capitol Street, NW, Washington, DC 20001 • 202/393-6599, Fax 202/638-3386

November 18, 2004

Office of Generic Drugs
Center for Drug Evaluation and Research
FOOD AND DRUG ADMINISTRATION
Document Control Room 150
Metro Park North II
7500 Standish Place
Rockville, Maryland 20855-2773

N/xp

PATENT AMENDMENT

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NIACIN EXTENDED RELEASE TABLETS, 1000 MG

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Sincerely,
BARR LABORATORIES, INC.

Nicholas Tantillo (ag)

Nicholas Tantillo
Senior Director Regulatory Affairs

CDR stamp date not known
'229 patent listed in
OB 12/20/2004
per C. Bina 2/11/2005

Barr Laboratories, Inc.

Suite 722, 444 North Capitol Street, NW, Washington, DC 20001 • 202/393-6599, Fax 202/638-3386

November 19, 2004

ORIG AMENDMENT
N | XP

Office of Generic Drugs
Center for Drug Evaluation and Research
FOOD AND DRUG ADMINISTRATION
Document Control Room 150
Metro Park North II
7500 Standish Place
Rockville, Maryland 20855-2773

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Sincerely,
BARR LABORATORIES, INC.

Nicholas Tantillo (fa)

Nicholas Tantillo
Senior Director Regulatory Affairs

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NOV 2 2 2004
OGD / CDER

CDR stamp date not known
'229 patent listed in
OB 12/20/2004
per C. Bina 2/11/2005

Barr Laboratories, Inc.

Suite 722, 444 North Capitol Street, NW, Washington, DC 20001 • 202/393-6599, Fax 202/638-3386

November 22, 2004

Office of Generic Drugs
Center for Drug Evaluation and Research
FOOD AND DRUG ADMINISTRATION
Document Control Room 150
Metro Park North II
7500 Standish Place
Rockville, Maryland 20855-2773

ORIG AMENDMENT
N\XP

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Sincerely,
BARR LABORATORIES, INC.

Nicholas Tantillo (for)

Nicholas Tantillo
Senior Director Regulatory Affairs

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NOV 2 2 2004
OGD / CDER

CDR stamp date not known
'229 patent listed in
OB 12/20/2004
per C. Bina 2/11/2005

Barr Laboratories, Inc.

Suite 722, 444 North Capitol Street, NW, Washington, DC 20001 • 202/393-6599, Fax 202/638-3580

November 23, 2004

Office of Generic Drugs
Center for Drug Evaluation and Research
FOOD AND DRUG ADMINISTRATION
Document Control Room 150
Metro Park North II
7500 Standish Place
Rockville, Maryland 20855-2773

N/xP

PATENT AMENDMENT

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Sincerely,
BARR LABORATORIES, INC.

Nicholas Tantillo (fa)

Nicholas Tantillo
Senior Director Regulatory Affairs

CDR stamp date not known
'229 patent listed in
OB 12/20/2004
per C. Bina 2/11/2005

Barr Laboratories, Inc.

Suite 722, 444 North Capitol Street, NW, Washington, DC 20001 • 202/393-6599, Fax 202/638-3386

November 24, 2004

Office of Generic Drugs
Center for Drug Evaluation and Research
FOOD AND DRUG ADMINISTRATION
Document Control Room 150
Metro Park North II
7500 Standish Place
Rockville, Maryland 20855-2773

N/xP

PATENT AMENDMENT

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If you have any questions concerning this application, please contact me by phone at (201) 930-3650 or by fax at (201) 930-3318.

Sincerely,
BARR LABORATORIES, INC.

Nicholas Tantillo (fx)

Nicholas Tantillo
Senior Director Regulatory Affairs

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NOV 23 2004
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RECEIVED
NOV 24 2004
OGD / CDER

CDR stamp date not known
'229 patent listed in
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per C. Bina 2/11/2005

Barr Laboratories, Inc.

Suite 722, 444 North Capitol Street, NW, Washington, DC 20001 • 202/393-6599, Fax 202/638-3386

November 26, 2004

N/xP

Office of Generic Drugs
Center for Drug Evaluation and Research
FOOD AND DRUG ADMINISTRATION
Document Control Room 150
Metro Park North II
7500 Standish Place
Rockville, Maryland 20855-2773

PATENT AMENDMENT

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Sincerely,
BARR LABORATORIES, INC.

Nicholas Tantillo (sa)

Nicholas Tantillo
Senior Director Regulatory Affairs

Barr Laboratories, Inc.

ORIGINAL

4-1

Suite 722, 444 North Capitol Street, NW, Washington, DC 20001 • 202/393-6599, Fax 202/638-3386

November 29, 2004

Office of Generic Drugs
Center for Drug Evaluation and Research
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Document Control Room 150
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7500 Standish Place
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N/XP

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Sincerely,
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Nicholas Tantillo

Nicholas Tantillo
Senior Director Regulatory Affairs

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per C. Bina 2/11/2005

Barr Laboratories, Inc.

Suite 722, 444 North Capitol Street, NW, Washington, DC 20001 • 202/393-6599, Fax 202/638-3386

November 30, 2004

Office of Generic Drugs
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ORIG AMENDMENT
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Nicholas Tantillo

Nicholas Tantillo
Senior Director Regulatory Affairs

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per C. Bina 2/11/2005

Barr Laboratories, Inc.

Suite 722, 444 North Capitol Street, NW, Washington, DC 20001 • 202/393-6599, Fax 202/638-3386

December 1, 2004

Office of Generic Drugs
Center for Drug Evaluation and Research
FOOD AND DRUG ADMINISTRATION
Document Control Room 150
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PATENT AMENDMENT

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Barr Laboratories will give the required notice under 21 CFR 314.95(a) to KOS Pharmaceuticals Inc., the NDA holder and the owner of U.S. Patent No. 6818229.

If you have any questions concerning this application, please contact me by phone at (201) 930-3650 or by fax at (201) 930-3318.

Sincerely,
BARR LABORATORIES, INC.

Nicholas Tantillo

Nicholas Tantillo
Senior Director Regulatory Affairs

CDR stamp date not known
'229 patent listed in
OB 12/20/2004
per C. Bina 2/11/2005

4.1

Barr Laboratories, Inc.

Suite 722, 444 North Capitol Street, NW, Washington, DC 20001 • 202/393-6599, Fax 202/638-3386

December 2, 2004

Office of Generic Drugs
Center for Drug Evaluation and Research
FOOD AND DRUG ADMINISTRATION
Document Control Room 150
Metro Park North II
7500 Standish Place
Rockville, Maryland 20855-2773

N/XP

PATENT AMENDMENT

REFERENCE: ANDA 76-250
NIACIN EXTENDED RELEASE TABLETS, 1000 MG

Reference is made to our Abbreviated New Drug Application dated October 2, 2001, submitted under Section 505(j) of the Federal Food and Cosmetic Act by Barr Laboratories, Inc. for Niacin Extended Release Tablets, 1000 mg.

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If you have any questions concerning this application, please contact me by phone at (201) 930-3650 or by fax at (201) 930-3318.

Sincerely,
BARR LABORATORIES, INC.

Nicholas Tantillo (fax)

Nicholas Tantillo
Senior Director Regulatory Affairs

CDR stamp date not known
'229 patent listed in
OB 12/20/2004
per C. Bina 2/11/2005

Barr Laboratories, Inc.

Suite 722, 444 North Capitol Street, NW, Washington, DC 20001 - 202/393-6599, Fax 202/638-3386

December 3, 2004

Office of Generic Drugs
Center for Drug Evaluation and Research
FOOD AND DRUG ADMINISTRATION
Document Control Room 150
Metro Park North II
7500 Standish Place
Rockville, Maryland 20855-2773

N/XP

PATENT AMENDMENT

REFERENCE: ANDA 76-250
NIACIN EXTENDED RELEASE TABLETS, 1000 MG

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If you have any questions concerning this application, please contact me by phone at (201) 930-3650 or by fax at (201) 930-3318.

Sincerely,
BARR LABORATORIES, INC.

Nicholas Tantillo

Nicholas Tantillo
Senior Director Regulatory Affairs

CDR stamp date not known
'229 patent listed in
OB 12/20/2004
per C. Bina 2/11/2005

Barr Laboratories, Inc.

Suite 722, 444 North Capitol Street, NW, Washington, DC 20001 • 202/393-6599, Fax 202/638-3386

December 6, 2004

Office of Generic Drugs
Center for Drug Evaluation and Research
FOOD AND DRUG ADMINISTRATION
Document Control Room 150
Metro Park North II
7500 Standish Place
Rockville, Maryland 20855-2773

NEW CORRESP
XP

PATENT AMENDMENT

REFERENCE: ANDA 76-250
NIACIN EXTENDED RELEASE TABLETS, 1000 MG

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If you have any questions concerning this application, please contact me by phone at (201) 930-3650 or by fax at (201) 930-3318.

Sincerely,
BARR LABORATORIES, INC.

Nicholas Tantillo
Senior Director Regulatory Affairs

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'229 patent listed in
OB 12/20/2004
per C. Bina 2/11/2005

Barr Laboratories, Inc.

Suite 722, 444 North Capitol Street, NW, Washington, DC 20001 • 202/393-6599, Fax 202/638-3386

December 7, 2004

Office of Generic Drugs
Center for Drug Evaluation and Research
FOOD AND DRUG ADMINISTRATION
Document Control Room 150
Metro Park North II
7500 Standish Place
Rockville, Maryland 20855-2773

N/cP

PATENT AMENDMENT

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If you have any questions concerning this application, please contact me by phone at (201) 930-3650 or by fax at (201) 930-3318.

Sincerely,
BARR LABORATORIES, INC.

Nicholas Tantillo (fax)

Nicholas Tantillo
Senior Director Regulatory Affairs

CDR stamp date not known
'229 patent listed in
OB 12/20/2004
per C. Bina 2/11/2005

Barr Laboratories, Inc.

Suite 722, 444 North Capitol Street, NW, Washington, DC 20001 • 202/393-6599, Fax 202/638-3386

December 8, 2004

Office of Generic Drugs
Center for Drug Evaluation and Research
FOOD AND DRUG ADMINISTRATION
Document Control Room 150
Metro Park North II
7500 Standish Place
Rockville, Maryland 20855-2773

XP

PATENT AMENDMENT

REFERENCE: ANDA 76-250
NIACIN EXTENDED RELEASE TABLETS, 1000 MG

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If you have any questions concerning this application, please contact me by phone at (201) 930-3650 or by fax at (201) 930-3318.

Sincerely,
BARR LABORATORIES, INC.

Nicholas Tantillo (fa)

Nicholas Tantillo
Senior Director Regulatory Affairs

CDR stamp date not known
'229 patent listed in
OB 12/20/2004
per C. Bina 2/11/2005

Barr Laboratories, Inc.

Suite 722, 444 North Capitol Street, NW, Washington, DC 20001 • 202/393-6599, Fax 202/638-3386

December 9, 2004

Office of Generic Drugs
Center for Drug Evaluation and Research
FOOD AND DRUG ADMINISTRATION
Document Control Room 150
Metro Park North II
7500 Standish Place
Rockville, Maryland 20855-2773

N/xP

PATENT AMENDMENT

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Sincerely,
BARR LABORATORIES, INC.

Nicholas Tantillo (FAX)

Nicholas Tantillo
Senior Director Regulatory Affairs

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DEC 09 2004
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CDR stamp date not known
'229 patent listed in
OB 12/20/2004
per C. Bina 2/11/2005

Barr Laboratories, Inc.

Suite 722, 444 North Capitol Street, NW, Washington, DC 20001 • 202/393-6599, Fax 202/638-3386

XP

December 10, 2004

Office of Generic Drugs
Center for Drug Evaluation and Research
FOOD AND DRUG ADMINISTRATION
Document Control Room 150
Metro Park North II
7500 Standish Place
Rockville, Maryland 20855-2773

PATENT AMENDMENT

REFERENCE: ANDA 76-250
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If you have any questions concerning this application, please contact me by phone at (201) 930-3650 or by fax at (201) 930-3318.

Sincerely,
BARR LABORATORIES, INC.

Nicholas Tantillo
Senior Director Regulatory Affairs

CDR stamp date not known
'229 patent listed in
OB 12/20/2004
per C. Bina 2/11/2005

Barr Laboratories, Inc.

Suite 722, 444 North Capitol Street, NW, Washington, DC 20001 • 202/393-6599, Fax 202/638-3386

December 13, 2004

N/xP

Office of Generic Drugs
Center for Drug Evaluation and Research
FOOD AND DRUG ADMINISTRATION
Document Control Room 150
Metro Park North II
7500 Standish Place
Rockville, Maryland 20855-2773

PATENT AMENDMENT

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If you have any questions concerning this application, please contact me by phone at (201) 930-3650 or by fax at (201) 930-3318.

Sincerely,
BARR LABORATORIES, INC.

Nicholas Tantillo (OA)

Nicholas Tantillo
Senior Director Regulatory Affairs

CDR stamp date not known
'229 patent listed in
OB 12/20/2004
per C. Bina 2/11/2005

Barr Laboratories, Inc.

Suite 722, 444 North Capitol Street, NW, Washington, DC 20001 • 202/393-6599, Fax 202/638-3386

December 14, 2004

Office of Generic Drugs
Center for Drug Evaluation and Research
FOOD AND DRUG ADMINISTRATION
Document Control Room 150
Metro Park North II
7500 Standish Place
Rockville, Maryland 20855-2773

N/xP

PATENT AMENDMENT

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If you have any questions concerning this application, please contact me by phone at (201) 930-3650 or by fax at (201) 930-3318.

Sincerely,
BARR LABORATORIES, INC.

Nicholas Tantillo
Senior Director Regulatory Affairs

CDR stamp date not known
'229 patent listed in
OB 12/20/2004
per C. Bina 2/11/2005

Barr Laboratories, Inc.

3 1

Suite 722, 444 North Capitol Street, NW, Washington, DC 20001 • 202/393-6599, Fax 202/638-3386

December 15, 2004

Office of Generic Drugs
Center for Drug Evaluation and Research
FOOD AND DRUG ADMINISTRATION
Document Control Room 150
Metro Park North II
7500 Standish Place
Rockville, Maryland 20855-2773

N/XP

PATENT AMENDMENT

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NIACIN EXTENDED RELEASE TABLETS, 1000 MG

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If you have any questions concerning this application, please contact me by phone at (201) 930-3650 or by fax at (201) 930-3318.

Sincerely,
BARR LABORATORIES, INC.

Nicholas Tantillo (SA)

Nicholas Tantillo
Senior Director Regulatory Affairs

CDR stamp date not known
'229 patent listed in
OB 12/20/2004
per C. Bina 2/11/2005

Barr Laboratories, Inc.

Suite 722, 444 North Capitol Street, NW, Washington, DC 20001 • 202/393-6599, Fax 202/638-3386

December 16, 2004

Office of Generic Drugs
Center for Drug Evaluation and Research
FOOD AND DRUG ADMINISTRATION
Document Control Room 150
Metro Park North II
7500 Standish Place
Rockville, Maryland 20855-2773

N/XP

PATENT AMENDMENT

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NIACIN EXTENDED RELEASE TABLETS, 1000 MG

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Sincerely,
BARR LABORATORIES, INC.

Nicholas Tantillo
Senior Director Regulatory Affairs

RECEIVED
DEC 16 2004
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CDR stamp date not known
'229 patent listed in
OB 12/20/2004
per C. Bina 2/11/2005

Barr Laboratories, Inc.

Suite 722, 444 North Capitol Street, NW, Washington, DC 20001 • 202/393-6599, Fax 202/638-3386

December 17, 2004

Office of Generic Drugs
Center for Drug Evaluation and Research
FOOD AND DRUG ADMINISTRATION
Document Control Room 150
Metro Park North II
7500 Standish Place
Rockville, Maryland 20855-2773

N/xP

PATENT AMENDMENT

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NIACIN EXTENDED RELEASE TABLETS, 1000 MG

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If you have any questions concerning this application, please contact me by phone at (201) 930-3650 or by fax at (201) 930-3318.

Sincerely,
BARR LABORATORIES, INC.

Nicholas Tantillo (fax)

Nicholas Tantillo
Senior Director Regulatory Affairs

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Barr Laboratories, Inc.

Suite 722, 444 North Capitol Street, NW, Washington, DC 20001 • 202/393-6599, Fax 202/638-3386

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December 20, 2004

N/XP

Office of Generic Drugs
Center for Drug Evaluation and Research
FOOD AND DRUG ADMINISTRATION
Document Control Room 150
Metro Park North II
7500 Standish Place
Rockville, Maryland 20855-2773

PATENT AMENDMENT

REFERENCE: ANDA 76-250
NIACIN EXTENDED RELEASE TABLETS, 1000 MG

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Sincerely,
BARR LABORATORIES, INC.

Nicholas Tantillo (fa)

Nicholas Tantillo
Senior Director Regulatory Affairs

CDR stamp date not known
'229 patent listed in
OB 12/20/2004
per C. Bina 2/11/2005

Barr Laboratories, Inc.

Suite 722, 444 North Capitol Street, NW, Washington, DC 20001 • 202/393-6599, Fax 202/638-3386

December 21, 2004

+P

Office of Generic Drugs
Center for Drug Evaluation and Research
FOOD AND DRUG ADMINISTRATION
Document Control Room 150
Metro Park North II
7500 Standish Place
Rockville, Maryland 20855-2773

PATENT AMENDMENT

REFERENCE: ANDA 76-250
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Sincerely,
BARR LABORATORIES, INC.

Nicholas Tantillo (FAX)

Nicholas Tantillo
Senior Director Regulatory Affairs

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DEC 2 1 2004
OGD / CDER

CDR stamp date not known
'229 patent listed in
OB 12/20/2004
per C. Bina 2/11/2005
RR for '229 dated 1/10/05. bnf

Barr Laboratories, Inc.

2 Quaker Road • P.O. Box 2900 • Pomona, NY 10970-0519 • 845/362-1100

January 28, 2005

ORIG AMENDMENT
N 1XP

Office of Generic Drugs
Center for Drug Evaluation and Research
FOOD AND DRUG ADMINISTRATION
Document Control Room 150
Metro Park North II
7500 Standish Place
Rockville, Maryland 20855-2773

PATENT AMENDMENT

REFERENCE: ANDA 76-250
NIACIN EXTENDED RELEASE TABLETS, 1000 MG

Reference is made to our Abbreviated New Drug Application dated October 2, 2001, submitted under Section 505(j) of the Federal Food and Cosmetic Act by Barr Laboratories, Inc. for Niacin Extended Release Tablets, 1000 mg.

In accordance with our Patent Certification Statement submitted on December 21, 2004 under 21 CFR §314.95(a) and (d), notice was sent by certified mail on December 21, 2004 return receipt requested to the owner of U.S. Patent No. 6,818,229 which is the subject of the certification and to the holder of the approved application under Section 505(b) of the Act.

In accordance with 21 CFR §314.95(d), Barr is hereby submitting a Patent Amendment to certify that notice was provided to KOS Pharmaceuticals, Inc. (Owner of the patent and NDA holder) by Sterne, Kessler, Goldstein and Fox P.L.L.C on behalf of Barr Laboratories Inc.

The contents of the notice letter comply with 21 CFR §314.95(c). The notice letter cites the appropriate section of the Act. In this notice letter, Barr alleges that in its opinion U.S. Patent No. 6,818,229 is invalid, unenforceable or will not be infringed by the manufacture, use, or sale of Barr's Niacin Extended Release Tablets, 1000 mg.

In accordance with 21 CFR §314.95(e), enclosed please find a copy of the return receipt from KOS Pharmaceuticals, Inc. for the notice, which was delivered on January 10, 2005.

If you have any questions concerning this patent amendment, please contact me by phone at (201) 930-3650 or by fax at (201) 930-3318.

Sincerely,
BARR LABORATORIES, INC.

Nicholas Tantillo
Senior Director, Regulatory Affairs

APPEARS THIS WAY
ON ORIGINAL

Barr Laboratories, Inc.

2 Quaker Road • P.O. Box 2900 • Pomona, NY 10970-0519 • 845/362-1100

ORIG AMENDMENT

January 28, 2005

Office of Generic Drugs
Center for Drug Evaluation and Research
FOOD AND DRUG ADMINISTRATION
Document Control Room 150
Metro Park North II
7500 Standish Place
Rockville, Maryland 20855-2773

N/A

MINOR AMENDMENT - FINAL APPROVAL REQUESTED

REFERENCE: ANDA 76-250
NIACIN EXTENDED RELEASE TABLETS, 1000 MG

Reference is made to our Abbreviated New Drug Application dated October 2, 2001, submitted by Barr Laboratories, Inc. (Barr) under Section 505(j) of the Federal Food, Drug, and Cosmetic Act, for Niacin Extended Release Tablets, 1000 mg.

Reference is also made to the Agency's May 9, 2003 tentative approval letter for this application in which you instructed us to submit a MINOR AMENDMENT – FINAL APPROVAL REQUESTED between 60 to 90 days prior to the date we believe that our application will be eligible for final approval. The Agency also requested that this amendment should provide updated information related to final – printed labeling or chemistry, manufacturing and control data, or any other changed in the conditions outlined in this abbreviated application.

As you instructed, we are amending this application with the following information:

1. In Barr's patent amendment dated December 9, 2002, we informed the FDA that KOS, the NDA holder and patent owner, received notice relating to U.S. Patent No 6,406,715 (the '715 patent) on September 30, 2002, and that KOS filed a complaint in the U.S. District Court, Southern District of New York.

   Barr's notice relating to the '715 patent forms the basis for a 30-month period that began on September 30, 2002 and will end on March 30, 2005. ANDA 76-378 will be eligible for final approval when this 30-month period ends on March 30, 2005.

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2. Labeling-The brochure has been revised to include the changes contained in the labeling approved on January 31, 2003 for Niaspan® NDA No. 20-381. In addition, the storage statement on the container label has been changed to match the storage statement in the brochure. Final printed labeling (electronic submission) is provided in this minor amendment.

3. Finished Product Release Testing-Barr has incorporated the use of the ——— ——— Dissolution System into the finished product testing. Copies of the revised test method and validation report are provided in this minor amendment.

4. Packaging-In accordance with the Guidance for Industry, "Changes to an Approved NDA or ANDA", dated April 2004, Section IX (D)(4), Barr is revising the currently approved metal cap with an equivalent plastic ———[1] cap. Please note that according to the Guidance referenced above, this change is Annual reportable and the supporting documentation is being submitted with this minor amendment in accordance with the instructions provided in the tentative approval letter. Barr commits to placing the first batch in the controlled room stability program and submitting the data in the annual report.

Barr Laboratories, Inc. declares that the electronic information contained in the enclosed CD-ROM is virus-free and was checked by using Symantec's AntiVirus Corporate Editions Software (version 1/27/05 rev. 23). Barr Laboratories, Inc. also declares that all original signed paper certifications have been provided in original paper form.

If you have any questions concerning this amendment, please contact me by phone at (201) 930-3650 or by fax at (201) 930-3318.

Sincerely,
BARR LABORATORIES, INC.

Nicholas Tantillo
Senior Director,
Regulatory Affairs

Cc: Martin Shimer, Branch Chief, Regulatory Support Branch (facsimile)

Barr Laboratories, Inc.

2 Quaker Road • P.O. Box 2900 • Pomona, NY 10970-0519 • 845/362-1100

March 4, 2005

Office of Generic Drugs
Center for Drug Evaluation and Research
FOOD AND DRUG ADMINISTRATION
Document Control Room 150
Metro Park North II
7500 Standish Place
Rockville, Maryland 20855-2773

ORIG AMENDMENT
N / Am

TELEPHONE AMENDMENT

REFERENCE: ANDA 76-250
NIACIN EXTENDED RELEASE TABLETS, 1000 MG

Reference is made to our Abbreviated New Drug Application dated October 2, 2001, submitted by Barr Laboratories, Inc. (Barr) under Section 505(j) of the Federal Food, Drug, and Cosmetic Act, for Niacin Extended Release Tablets, 1000 mg.

Reference is also made to the February 18, 2005 and March 3, 2005 teleconference between Dr. Albert Mueller, Team Leader, Dr. Bing Cai, Reviewer from Division of Chemistry Team 1, and Benjamin Danso, Project Manager OGD with Sharif Ahmed, Associate Director, Regulatory Affairs Barr Laboratories, Inc. The following comments were discussed. The Agency advised that the response should be submitted as a Telephone Amendment:

Comment 1:
The Agency suggests that you revise the specifications for the drug substance and the drug product to be consistent with the ICH recommendations as specified in Q3A and Q3B.

Response 1:
Niacin is a USP article with a specification for total impurities of NMT 2.0% as defined in USP <466>. Barr's current specification is consistent with USP.

It should be noted that in the Draft Guidance, "ANDAs: Impurities in Drug Substances" dated January 2005, it is stated that "This guidance does not apply to DMFs referenced in ANDAs or ANDA supplements if the FDA has already accepted a DMF for that dosage form, route of administration, and daily intake prior to publication of the final version of this guidance." Barr has obtained confirmation from —— the approved API supplier, that their DMF for Niacin is already referenced in an approved NDA.

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MAR 7 2005
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However, Barr is working with vendor to add a new—— test and an individual unspecified specification of NMT——%. The method was developed and validated by the vendor. They are in the process of having the documents translated into English to support an amendment to their DMF. This issue was discussed during a second teleconference between Dr. Albert Mueller, Dr. Bing Cai, Benjamin Danso, and Sharif Ahmed on March 3, 2005. During this teleconference it was agreed that a commitment to submit the revised specification, test method and method validation in a Changes Being Effected Supplement would be acceptable.

Based on the above discussion with the Agency, Barr commits to the following:

1. Add a new —— test for impurities with a specification for unspecified impurities of NMT——% in accordance with ICH Q3A(R).

2. Submit the revised test method and specification in a Supplement-Changes Being Effected in accordance with Section VIII (C)(2)(a) of the Guidance for Industry, "Changes to an Approved NDA or ANDA", dated April 2004 as it provides increased assurance that the drug product will have the identity, strength, quality, purity, or potency that it purports to posses.

3. Submit the complete method validation by —— along with Barr's evaluation of the method in the supplement.

As requested by the Agency and in accordance with the ICH Q3B(R) guidance the specification for individual impurities in the finished product has been revised from NMT ——% to NMT ——%. A copy of the revised specification sheets and test method are provided.

Comment 2:
In the method validation report for the drug release, there is a statement regarding the inability to use ——————————. Please clarify.

Response 2:

Identical copies of this amendment have been sent to the New York and Baltimore district offices of the FDA. A document certification is attached.

If you have any questions concerning this amendment, please contact me by phone at (201) 930-3650 or by fax at (201) 930-3318.

Sincerely,
BARR LABORATORIES, INC.

Nicholas Tantillo
Senior Director,
Regulatory Affairs

CC: Benjamin Danso, project manager OGD, facsimile (301) 594-0180

Barr Laboratories, Inc.

2 Quaker Road • P.O. Box 2900 • Pomona, NY 10970-0519 • 845/362-1100

March 4, 2005

N/XP

Office of Generic Drugs
Center for Drug Evaluation and Research
FOOD AND DRUG ADMINISTRATION
Document Control Room 150
Metro Park North II
7500 Standish Place
Rockville, Maryland 20855-2773

PATENT AMENDMENT

REFERENCE: ANDA 76-250
NIACIN EXTENDED RELEASE TABLETS, 1000 MG

Reference is made to our Abbreviated New Drug Application dated October 2, 2001, submitted under Section 505(j) of the Federal Food and Cosmetic Act by Barr Laboratories, Inc. for Niacin Extended Release Tablets, 1000 mg.

In accordance with our Patent Certification Statement submitted on January 28, 2005 under 21 CFR §314.95(a) and (d), notice was sent by certified mail on December 21, 2004 return receipt requested to the owner of U.S. Patent No. 6,818,229 which is the subject of the certification and to the holder of the approved application under Section 505(b) of the Act.

Barr is hereby submitting a Patent Amendment to certify that the 45-day period, as provided for in section 505 (j)(4)(B)(iii) of the Act, to initiate litigation has expired. No complaint regarding U.S. Patent No. 6,818,229 has been filed by KOS Pharmaceuticals, Inc. within the statutory period.

If you have any questions concerning this patent amendment, please contact me by phone at (201) 930-3650 or by fax at (201) 930-3318.

Sincerely,
BARR LABORATORIES, INC.

Nicholas Tantillo
Senior Director, Regulatory Affairs

Barr Laboratories, Inc.

2 Quaker Road • P.O. Box 2900 • Pomona, NY 10970-0519 • 845/362-1100

March 11, 2005

Office of Generic Drugs
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N/AM

ORIG AMENDMENT

TELEPHONE AMENDMENT

REFERENCE: ANDA 76-250
NIACIN EXTENDED RELEASE TABLETS, 1000 MG

Reference is made to our Abbreviated New Drug Application dated October 2, 2001, submitted by Barr Laboratories, Inc. (Barr) under Section 505(j) of the Federal Food, Drug, and Cosmetic Act, for Niacin Extended Release Tablets, 1000 mg.

Reference is also made to the March 9, 2005 teleconference between, Dr. Paul Schwartz, Dr. Albert Mueller, Dr. Bing Cai, and Benjamin Danso, from the Agency and Sharif Ahmed, from Barr Laboratories, Inc. The following comment was discussed. The Agency advised that the response should be submitted as a Telephone Amendment:

Comment 1:

In addition to the drug product, the Agency requests Barr to revise the specifications for the drug substance to be consistent with the ICH recommendations as specified in Q3A(R) prior to approval.

Response 1:

As suggested by Dr. Paul Schwartz, Barr evaluated the validated test method for impurities in the finished product for the drug substance. Although the method was validated for the finished product, additional method validation was conducted to lower the limit of quantitation. Therefore, this method is considered suitable for the drug substance, as there is no potential for interference from any excipient.

Based on this evaluation and method validation, this procedure has been added to the drug substance test method. In accordance with ICH Q3A(R), a specification for individual unspecified impurity of NMT — % was added. Barr has also added a limit for total impurities of NMT — % for the drug substance (applicable to the —— method only).

Copies of the revised test method, specification sheet and the validation report are provided.

Identical copies of this amendment have been sent to the New York and Baltimore district offices of the FDA. A document certification is attached.

If you have any questions concerning this amendment, please contact me by phone at (201) 930-3650 or by fax at (201) 930-3318.

Sincerely,
BARR LABORATORIES, INC.

Nicholas Tantillo
Senior Director,
Regulatory Affairs

CC: Benjamin Danso, project manager OGD, facsimile (301) 594-0180

Barr Laboratories, Inc.

2 Quaker Road • P.O. Box 2900 • Pomona, NY 10970-0519 • 845/362-1100

April 14, 2005

Office of Generic Drugs
Center for Drug Evaluation and Research
FOOD AND DRUG ADMINISTRATION
Document Control Room 150
Metro Park North II
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Rockville, Maryland 20855-2773

MC

GENERAL CORRESPONDENCE

REFERENCE: ANDA 76-250
NIACIN EXTENDED RELEASE TABLETS, 1000 MG

Reference is made to our Abbreviated New Drug Application dated October 2, 2001, submitted by Barr Laboratories, Inc. (Barr) under Section 505(j) of the Federal Food, Drug, and Cosmetic Act, for Niacin Extended Release Tablets, 1000 mg.

Reference is also made to the April 14, 2005 teleconference between, Craig Kiester, from the Agency and Christine Mundkur, from Barr Laboratories, Inc. The following observation was discussed.

The commitment stating that Barr will work with the Agency to resolve any method validation issues and a statement that the USP methods are regulatory methods can not be located in the application.

In the March 25, 2002 minor amendment Barr stated "Barr commits to work with the Agency to expeditiously resolve any deficiencies from the Methods Validation study if the ANDA is approved prior to its completion". In addition, Barr would like to acknowledge that the USP methods are the regulatory methods. In the event of a dispute, the USP methods will prevail.

If you have any questions concerning this amendment, please contact me by phone at (201) 930-3650 or by fax at (201) 930-3318.

Sincerely,
BARR LABORATORIES, INC.

Nicholas Tantillo
Senior Director, Regulatory Affairs

CC: Craig Kiester, project manager OGD, facsimile (301) 594-0180