CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

NDA 21-204/S-006

Trade Name: Starlix Tablets

Generic Name: nateglinade

Sponsor: Novartis Pharmaceuticals Corporation

Approval Date: October 20, 2003

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APPLICATION NUMBER:

NDA 21-204/S-006

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APPLICATION NUMBER:

NDA 21-204/S-006

APPROVAL LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-204/S-006

Novartis Pharmaceuticals Corporation
Attention: Carl Schlotfeldt
Associate Director, Drug Regulatory Affairs
One Health Plaza
East Hanover, NJ 07936-1080

Dear Mr. Schlotfeldt:

Please refer to your supplemental new drug application dated December 19, 2002, received December 20, 2002, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Starlix® (nateglinide) Tablets.

We acknowledge receipt of your submissions dated March 31, June 17, July 24, and October 20, 2003 (electronic copy).

This supplemental new drug application provides for an expanded indication for the use of Starlix® (nateglinide) Tablets, in combination with antidiabetic drugs in the thiazolidinedione class.

We completed our review of this application, as amended. This application is approved, effective on the date of this letter, for use as recommended in the agreed-upon labeling text.

The final printed labeling (FPL) must be identical to the enclosed labeling for the package insert submitted October 20, 2003. Marketing the product with FPL that is not identical to the approved labeling text may render the product misbranded and an unapproved new drug.

Please submit the FPL electronically according to the guidance for industry titled Providing Regulatory Submissions in Electronic Format – NDA. Alternatively, you may submit 20 paper copies of the FPL as soon as it is available, in no case more than 30 days after it is printed. Please individually mount 15 of the copies on heavy-weight paper or similar material. For administrative purposes, this submission should be designated "FPL for approved supplement NDA 21-204/S-006." Approval of this submission by FDA is not required before the labeling is used.

If you issue a letter communicating important information about this drug product (i.e., a "Dear Health Care Professional" letter), we request that you submit a copy of the letter to this NDA and a copy to the following address:

MEDWATCH, HFD-410
FDA
5600 Fishers Lane
Rockville, MD 20857

We remind you that you must comply with reporting requirements for an approved NDA (21CFR 314.80 and 314.81).

If you have any questions, please call Ms. Jena Weber, Regulatory Project Manager, at 301-827-6422.

Sincerely,

{See appended electronic signature page}

David G. Orloff, M.D.
Director
Division of Metabolic and Endocrine Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Enclosure (package insert labeling – 11 pages)

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

David Orloff
10/20/03 01:28:02 PM

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 21-204/S-006

APPROVED LABELING

Starlix®

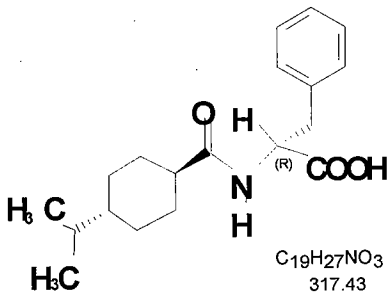
(nateglinide) tablets

Rx only

DESCRIPTION

STARLIX® (NATEGLINIDE) IS AN ORAL ANTIDIABETIC AGENT USED IN THE MANAGEMENT OF TYPE 2 DIABETES MELLITUS [ALSO KNOWN AS NON-INSULIN DEPENDENT DIABETES MELLITUS (NIDDM) OR ADULT-ONSET DIABETES]. STARLIX, (-)-N-[(TRANS-4-ISOPROPYLCYCLOHEXANE)CARBONYL]-D-PHENYLALANINE, IS STRUCTURALLY UNRELATED TO THE ORAL SULFONYLUREA INSULIN SECRETAGOGUES.

The structural formula is as shown



Nateglinide is a white powder with a molecular weight of 317.43. It is freely soluble in methanol, ethanol, and chloroform, soluble in ether, sparingly soluble in acetonitrile and octanol, and practically insoluble in water. Starlix biconvex tablets contain 60mg, or 120 mg, of nateglinide for oral administration.

Inactive ingredients: colloidal silicon dioxide, croscarmellose sodium, hydroxypropyl methylcellulose, iron oxides (red or yellow), lactose monohydrate, magnesium stearate, microcrystalline cellulose, polyethylene glycol, povidone, talc, and titanium dioxide .

CLINICAL PHARMACOLOGY

Mechanism of Action

Nateglinide is an amino-acid derivative that lowers blood glucose levels by stimulating insulin secretion from the pancreas. This action is dependent upon functioning beta-cells in the pancreatic islets. Nateglinide interacts with the ATP-sensitive potassium ($K+_{ATP}$) channel on pancreatic beta-cells. The subsequent depolarization of the beta cell opens the calcium channel, producing calcium influx and insulin secretion. The extent of insulin release is glucose dependent and diminishes at low glucose levels. Nateglinide is highly tissue selective with low affinity for heart and skeletal muscle.

Pharmacokinetics

Absorption

Following oral administration immediately prior to a meal, nateglinide is rapidly absorbed with mean peak plasma drug concentrations (C_{max}) generally occurring within 1 hour (T_{max}) after dosing. When administered to patients with Type 2 diabetes over the dosage range 60 mg to 240 mg three times a day for one week, nateglinide demonstrated linear pharmacokinetics for both AUC (area under the time/plasma concentration curve) and C_{max}. T_{max} was also found to be independent of dose in this patient population. Absolute bioavailability is estimated to be approximately 73%. When given with or after meals, the extent of nateglinide absorption (AUC) remains unaffected. However, there is a delay in the rate of absorption characterized by a decrease in C_{max} and a delay in time to peak plasma concentration (T_{max}). Plasma profiles are characterized by multiple plasma concentration peaks when nateglinide is administered under fasting conditions. This effect is diminished when nateglinide is taken prior to a meal.

Distribution

Based on data following intravenous (IV) administration of nateglinide, the steady state volume of distribution of nateglinide is estimated to be approximately 10 liters in healthy subjects. Nateglinide is extensively bound (98%) to serum proteins, primarily serum albumin, and to a lesser extent α_1 acid glycoprotein. The extent of serum protein binding is independent of drug concentration over the test range of 0.1-10 μg/mL.

Metabolism

Nateglinide is metabolized by the mixed-function oxidase system prior to elimination. The major routes of metabolism are hydroxylation followed by glucuronide conjugation. The major metabolites are less potent antidiabetic agents than nateglinide. The isoprene minor metabolite possesses potency similar to that of the parent compound nateglinide.

In vitro data demonstrate that nateglinide is predominantly metabolized by cytochrome P_{450} isoenzymes CYP2C9 (70%) and CYP3A4 (30%).

Excretion

Nateglinide and its metabolites are rapidly and completely eliminated following oral administration. Within 6 hours after dosing, approximately 75% of the administered ^{14}C-nateglinide was recovered in the urine. Eighty-three percent of the ^{14}C-nateglinide was excreted in the urine with an additional 10% eliminated in the feces. Approximately 16% of the ^{14}C-nateglinide was excreted in the urine as parent compound. In all studies of healthy volunteers and patients with Type 2 diabetes, nateglinide plasma concentrations declined rapidly with an average elimination half-life of approximately 1.5 hours. Consistent with this short elimination half-life, there was no apparent accumulation of nateglinide upon multiple dosing of up to 240 mg three times daily for 7 days.

Drug Interactions

In vitro drug metabolism studies indicate that Starlix is predominantly metabolized by the cytochrome P450 isozyme CYP2C9 (70%) and to a lesser extent CYP3A4 (30%). Starlix is a potential inhibitor of the CYP2C9 isoenzyme *in vivo* as indicated by its ability to inhibit the *in vitro* metabolism of tolbutamide. Inhibition of CYP 3A4 metabolic reactions was not detected in *in vitro* experiments.

Glyburide: In a randomized, multiple-dose crossover study, patients with Type 2 diabetes were administered 120 mg Starlix three times a day before meals for 1 day in combination with glyburide 10 mg daily. There were no clinically relevant alterations in the pharmacokinetics of either agent.

Metformin: When Starlix 120 mg three times daily before meals was administered in combination with metformin 500 mg three times daily to patients with Type 2 diabetes, there were no clinically relevant changes in the pharmacokinetics of either agent.

Digoxin: When Starlix 120 mg before meals was administered in combination with a single 1 mg dose of digoxin to healthy volunteers, there were no clinically relevant changes in the pharmacokinetics of either agent.

Warfarin: When healthy subjects were administered Starlix 120 mg three times daily before meals for four days in combination with a single dose of warfarin 30 mg on day 2, there were no alterations in the pharmacokinetics of either agent. Prothrombin time was not affected.

Diclofenac: Administration of morning and lunch doses of Starlix 120 mg in combination with a single 75 mg dose of diclofenac in healthy volunteers resulted in no significant changes to the pharmacokinetics of either agent.

Special Populations

Geriatric: Age did not influence the pharmacokinetic properties of nateglinide. Therefore, no dose adjustments are necessary for elderly patients.

Gender: No clinically significant differences in nateglinide pharmacokinetics were observed between men and women. Therefore, no dose adjustment based on gender is necessary.

Race: Results of a population pharmacokinetic analysis including subjects of Caucasian, black, and other ethnic origins suggest that race has little influence on the pharmacokinetics of nateglinide.

Renal Impairment: Compared to healthy matched subjects, patients with Type 2 diabetes and moderate to severe renal insufficiency (CrCl 15 - 50 mL/min) not on dialysis displayed similar apparent clearance, AUC, and Cmax. Patients with Type 2 diabetes and renal failure on dialysis exhibited reduced overall drug exposure. However, hemodialysis patients also experienced reductions in plasma protein binding compared to the matched healthy volunteers.

Hepatic Impairment: The peak and total exposure of nateglinide in non-diabetic subjects with mild hepatic insufficiency were increased by 30% compared to matched healthy subjects. Starlix® (nateglinide) should be used with caution in patients with chronic liver disease. (See PRECAUTIONS, Hepatic Impairment.)

Pharmacodynamics

Starlix is rapidly absorbed and stimulates pancreatic insulin secretion within 20 minutes of oral administration. When Starlix is dosed three times daily before meals there is a rapid rise in plasma insulin, with peak levels approximately 1 hour after dosing and a fall to baseline by 4 hours after dosing.

In a double-blind, controlled clinical trial in which Starlix was administered before each of three meals, plasma glucose levels were determined over a 12-hour, daytime period after 7 weeks of treatment. Starlix was administered 10 minutes before meals. The meals were based on standard diabetic weight maintenance menus with the total caloric content based on each subject's height. Starlix produced statistically significant decreases in fasting and post-prandial glycemia compared to placebo.

Clinical Studies

A total of 3,566 patients were randomized in nine double-blind, placebo- or active-controlled studies 8 to 24 weeks in duration to evaluate the safety and efficacy of Starlix® (nateglinice). 3,513 patients had efficacy values beyond baseline. In these studies Starlix was administered up to 30 minutes before each of three main meals daily.

Starlix Monotherapy Compared to Placebo

In a randomized, double-blind, placebo-controlled, 24-week study, patients with Type 2 diabetes with HbA_{1C} ≥6.8% on diet alone were randomized to receive either Starlix (60 mg or 120 mg three times daily before meals) or placebo. Baseline HbA_{1C} ranged from 7.9% to 8.1% and 77.8% of patients were previously untreated with oral antidiabetic therapy. Patients previously treated with antidiabetic medications were required to discontinue that medication for at least 2 months before randomization. The addition of Starlix before meals resulted in statistically significant reductions in mean HbA_{1C} and mean fasting plasma glucose (FPG) compared to placebo (See Table 1). The reductions in HbA_{1C} and FPG were similar for patients naïve to, and those previously exposed to, antidiabetic medications.

In this study, one episode of severe hypoglycemia (plasma glucose <36 mg/dL) was reported in a patient treated with Starlix 120 mg three times daily before meals. No patients experienced hypoglycemia that required third party assistance. Patients treated with Starlix had statistically significant mean increases in weight compared to placebo (Table 1).

In another randomized, double-blind, 24-week, active- and placebo-controlled study, patients with Type 2 diabetes were randomized to receive Starlix (120 mg three times daily before meals), metformin 500 mg (three times daily), a combination of Starlix 120 mg (three times daily before meals) and metformin 500 mg (three times daily), or placebo. Baseline HbA_{1C} ranged from 8.3% to 8.4%. Fifty-seven percent of patients were previously untreated with oral antidiabetic therapy. Starlix monotherapy resulted in significant reductions in mean HbA_{1C} and mean FPG compared to placebo that were similar to the results of the study reported above (See Table 2).

Table 1 Endpoint results for a 24-week, fixed dose study of Starlix monotherapy

	Placebo	Starlix 60 mg three times daily before meals	Starlix 120 mg three times daily before meals
HbA_{1c} (%)	*N=168*	*N=167*	*N=168*
Baseline (mean)	8.0	7.9	8.1
Change from baseline (mean)	+0.2	-0.3	-0.5
Difference from placebo (mean)		-0.5[a]	-0.7[a]
FPG (mg/dL)	*N=172*	*N=171*	*N=169*
Baseline (mean)	167.9	161.0	166.5
Change from baseline (mean)	+9.1	+0.4	-4.5
Difference from placebo (mean)		-8.7[a]	-13.6[a]
Weight (kg)	*N=170*	*N=169*	*N=166*
Baseline (mean)	85.8	83.7	86.3

Change from baseline (mean)	-0.7	+0.3	+0.9
Difference from placebo (mean)		+1.0[a]	+1.6[a]

[a] p-value ≤ 0.004.

Starlix Monotherapy Compared to Other Oral Antidiabetic Agents

Glyburide

In a 24-week, double-blind, active-controlled trial, patients with Type 2 diabetes who had been on a sulfonylurea for ≥ 3 months and who had a baseline HbA_{1C} ≥6.5% were randomized to receive Starlix (60 mg or 120 mg three times daily before meals) or glyburide 10 mg once daily. Patients randomized to Starlix had significant increases in mean HbA_{1C} and mean FPG at endpoint compared to patients randomized to glyburide.

Metformin

In another randomized, double-blind, 24-week, active- and placebo-controlled study, patients with Type 2 diabetes were randomized to receive Starlix (120 mg three times daily before meals), metformin 500 mg (three times daily), a combination of Starlix 120 mg (three times daily before meals) and metformin 500 mg (three times daily), or placebo. Baseline HbA_{1C} ranged from 8.3% to 8.4%. Fifty-seven percent of patients were previously untreated with oral antidiabetic therapy. The reductions in mean HbA_{1C} and mean FPG at endpoint with metformin monotherapy were significantly greater than the reductions in these variables with Starlix monotherapy. (See Table 2). Relative to placebo, Starlix monotherapy was associated with significant increases in mean weight whereas metformin monotherapy was associated with significant decreases in mean weight. Among the subset of patients naïve to antidiabetic therapy, the reductions in mean HbA_{1C} and mean FPG for Starlix monotherapy were similar to those for metformin monotherapy (See Table 2). Among the subset of patients previously treated with other antidiabetic agents, primarily glyburide, HbA_{1C} in the Starlix monotherapy group increased slightly from baseline, whereas HbA_{1C} was reduced in the metformin monotherapy group (See Table 2).

Starlix Combination Therapy

Metformin

In another randomized, double-blind, 24-week, active- and placebo-controlled study, patients with Type 2 diabetes were randomized to receive Starlix (120 mg three times daily before meals), metformin 500 mg (three times daily), a combination of Starlix 120 mg (three times daily before meals) and metformin 500 mg (three times daily), or placebo. Baseline HbA_{1C} ranged from 8.3% to 8.4%. Fifty-seven percent of patients were previously untreated with oral antidiabetic therapy. Patients previously treated with antidiabetic medications were required to discontinue medication for at least 2 months before randomization. The combination of Starlix and metformin resulted in statistically significantly greater reductions in HbA_{1C} and FPG compared to either Starlix or metformin monotherapy (see Table 2). Starlix, alone or in combination with metformin, significantly reduced the prandial glucose elevation from pre-meal to 2-hours post-meal compared to placebo and metformin alone.

In this study, one episode of severe hypoglycemia (plasma glucose ≤ 36 mg/dL) was reported in a patient receiving the combination of Starlix and metformin and four episodes of severe hypoglycemia were reported in a single patient in the metformin treatment arm. No patient experienced an episode of hypoglycemia that required third party assistance. Compared to placebo, Starlix monotherapy was

associated with a statistically significant increase in weight, while no significant change in weight was observed with combined Starlix and metformin therapy (See Table 2).

In another 24-week, double-blind, placebo-controlled trial, patients with Type 2 diabetes with $HbA_{1C} \geq$ 6.8% after treatment with metformin (≥ 1500 mg daily for ≥ 1 month) were first entered into a four week run-in period of metformin monotherapy (2000 mg daily) and then randomized to receive Starlix (60 or 120 mg three times daily before meals) or placebo in addition to metformin. Combination therapy with Starlix and metformin was associated with statistically significantly greater reductions in HbA_{1C} compared to metformin monotherapy (-0.4% and –0.6% for Starlix 60 mg and Starlix 120 mg plus metformin, respectively).

Table 2 Endpoint results for a 24-week study of Starlix monotherapy and combination with metformin

	Placebo	Starlix 120 mg three times daily before meals	Metformin 500 mg three times daily	Starlix 120 mg before meals plus Metformin*
HbA_{1c} (%)				
All	*N=160*	*N=171*	*N=172*	*N=162*
Baseline (mean)	8.3	8.3	8.4	8.4
Change from baseline (mean)	+0.4	-0.4 [bc]	-0.8 [c]	-1.5
Difference from placebo		-0.8 [a]	-1.2 [a]	-1.9 [a]
Naïve	*N=98*	*N=99*	*N=98*	*N=81*
Baseline (mean)	8.2	8.1	8.3	8.2
Change from baseline (mean)	+0.3	-0.7 [c]	-0.8 [c]	-1.6
Difference from placebo		*-1.0* [a]	*-1.1* [a]	*-1.9* [a]
Non-naïve	*N=62*	*N=72*	*N=74*	*N=81*
Baseline (mean)	8.3	8.5	8.7	8.7
Change from baseline (mean)	+0.6	+0.004 [bc]	-0.8 [c]	-1.4
Difference from placebo		-0.6 [a]	-1.4 [a]	-2.0 [a]
FPG (mg/dL)				
All	*N=166*	*N=173*	*N=174*	*N=167*
Baseline (mean)	194.0	196.5	196.0	197.7
Change from baseline (mean)	+8.0	-13.1 [bc]	-30.0 [c]	-44.9
Difference from placebo		-21.1 [a]	-38.0 [a]	-52.9 [a]
Weight (kg)				
All	*N=160*	*N=169*	*N=169*	*N=160*
Baseline (mean)	85.0	85.0	86.0	87.4
Change from baseline (mean)	-0.4	+0.9 [bc]	-0.1	+0.2
Difference from placebo		+1.3 [a]	+0.3	+0.6

[a] p-value ≤ 0.05 vs. placebo.
[b] p-value ≤ 0.03 vs. metformin.
[c] p-value ≤ 0.05 vs. combination.
* Metformin was administered three times daily

Rosiglitazone

A 24-Week, double blind multicenter, placebo-controlled trial was performed in patients with type 2 diabetes not adequately controlled after a therapeutic response to rosiglitazone monotherapy 8 mg daily. The addition of Starlix (120 mg three times per day with meals) was associated with statistically significantly greater reductions in HbA1c compared to rosiglitazone monotherapy. The difference was -0.77% at 24 weeks. The mean change in weight from baseline was about +3 kg for patients treated with Starlix plus rosiglitazone vs about +1 kg for patients treated with placebo plus rosiglitazone.

Glyburide

In a 12-week study of patients with Type 2 diabetes inadequately controlled on glyburide 10 mg once daily, the addition of Starlix (60 mg or 120 mg three times daily before meals) did not produce any additional benefit.

INDICATIONS AND USAGE

Starlix® (nateglinide) is indicated as monotherapy to lower blood glucose in patients with Type 2 diabetes (non-insulin dependent diabetes mellitus, NIDDM) whose hyperglycemia cannot be adequately controlled by diet and physical exercise and who have not been chronically treated with other anti-diabetic agents.

Starlix is also indicated for use in combination with metformin or a thiazolidinedione. In patients whose hyperglycemia is inadequately controlled with metformin, or after a therapeutic response to a thiazolidinedione, Starlix may be added to, but not substituted for, those drugs.

Patients whose hyperglycemia is not adequately controlled with glyburide or other insulin secretagogues should not be switched to Starlix, nor should Starlix be added to their treatment regimen.

CONTRAINDICATIONS

Starlix® (nateglinide) is contraindicated in patients with:

1. Known hypersensitivity to the drug or its inactive ingredients.
2. Type 1 diabetes.
3. Diabetic ketoacidosis. This condition should be treated with insulin.

PRECAUTIONS

Hypoglycemia: All oral blood glucose lowering drugs that are absorbed systemically are capable of producing hypoglycemia. The frequency of hypoglycemia is related to the severity of the diabetes, the level of glycemic control, and other patient characteristics. Geriatric patients, malnourished patients, and those with adrenal or pituitary insufficiency are more susceptible to the glucose lowering effect of these treatments. The risk of hypoglycemia may be increased by strenuous physical exercise, ingestion of alcohol, insufficient caloric intake on an acute or chronic basis, or combinations with other oral

antidiabetic agents. Hypoglycemia may be difficult to recognize in patients with autonomic neuropathy and/or those who use beta-blockers. Starlix® (nateglinide) should be administered prior to meals to reduce the risk of hypoglycemia. Patients who skip meals should also skip their scheduled dose of Starlix to reduce the risk of hypoglycemia.

Hepatic impairment: Starlix should be used with caution in patients with moderate-to-severe liver disease because such patients have not been studied.

Loss of glycemic control

Transient loss of glycemic control may occur with fever, infection, trauma, or surgery. Insulin therapy may be needed instead of Starlix therapy at such times. Secondary failure, or reduced effectiveness of Starlix over a period of time, may occur.

Information for Patients

Patients should be informed of the potential risks and benefits of Starlix and of alternative modes of therapy. The risks and management of hypoglycemia should be explained. Patients should be instructed to take Starlix 1 to 30 minutes before ingesting a meal, but to skip their scheduled dose if they skip the meal so that the risk of hypoglycemia will be reduced. Drug interactions should be discussed with patients. Patients should be informed of potential drug-drug interactions with Starlix.

Laboratory Tests

Response to therapies should be periodically assessed with glucose values and HbA_{1c} levels.

Drug Interactions

Nateglinide is highly bound to plasma proteins (98 %), mainly albumin. *In vitro* displacement studies with highly protein-bound drugs such as furosemide, propranolol, captopril, nicardipine, pravastatin, glyburide, warfarin, phenytoin, acetylsalicylic acid, tolbutamide, and metformin showed no influence on the extent of nateglinide protein binding. Similarly, nateglinide had no influence on the serum protein binding of propranolol, glyburide, nicardipine, warfarin, phenytoin, acetylsalicylic acid, and tolbutamide *in vitro*. However, prudent evaluation of individual cases is warranted in the clinical setting.

Certain drugs, including nonsteroidal anti-inflammatory agents (NSAIDs), salicylates, monoamine oxidase inhibitors, and non-selective beta-adrenergic-blocking agents may potentiate the hypoglycemic action of Starlix and other oral antidiabetic drugs.

Certain drugs including thiazides, corticosteroids, thyroid products, and sympathomimetics may reduce the hypoglycemic action of Starlix and other oral antidiabetic drugs.

When these drugs are administered to or withdrawn from patients receiving Starlix, the patient should be observed closely for changes in glycemic control.

Drug/Food Interactions

The pharmacokinetics of nateglinide were not affected by the composition of a meal (high protein, fat, or carbohydrate). However, peak plasma levels were significantly reduced when Starlix was administered 10 minutes prior to a liquid meal. Starlix did not have any effect on gastric emptying in healthy subjects as assessed by acetaminophen testing.

Carcinogenesis/Mutagenesis/Impairment of Fertility

Carcinogenicity: A two-year carcinogenicity study in Sprague-Dawley rats was performed with oral doses of nateglinide up to 900 mg/kg/day, which produced AUC exposures in male and female rats approximately 30 and 40 times the human therapeutic exposure respectively with a recommended Starlix dose of 120 mg, three times daily before meals. A two-year carcinogenicity study in B6C3F1 mice was performed with oral doses of nateglinide up to 400 mg/kg/day, which produced AUC exposures in male and female mice approximately 10 and 30 times the human therapeutic exposure with a recommended Starlix dose of 120 mg, three times daily before meals. No evidence of a tumorigenic response was found in either rats or mice.

Mutagenesis: Nateglinide was not genotoxic in the *in vitro* Ames test, mouse lymphoma assay, chromosome aberration assay in Chinese hamster lung cells, or in the *in vivo* mouse micronucleus test.

Impairment of Fertility: Fertility was unaffected by administration of nateglinide to rats at doses up to 600 mg/kg (approximately 16 times the human therapeutic exposure with a recommended Starlix dose of 120 mg three times daily before meals).

Pregnancy

Pregnancy Category C

Nateglinide was not teratogenic in rats at doses up to 1000 mg/kg (approximately 60 times the human therapeutic exposure with a recommended Starlix dose of 120 mg, three times daily before meals). In the rabbit, embryonic development was adversely affected and the incidence of gallbladder agenesis or small gallbladder was increased at a dose of 500 mg/kg (approximately 40 times the human therapeutic exposure with a recommended Starlix dose of 120 mg, three times daily before meals). There are no adequate and well-controlled studies in pregnant women. Starlix should not be used during pregnancy.

Labor and Delivery

The effect of Starlix on labor and delivery in humans is not known.

Nursing Mothers

Studies in lactating rats showed that nateglinide is excreted in the milk; the $AUC_{0\text{-}48h}$ ratio in milk to plasma was approximately 1:4. During the peri-and postnatal period body weights were lower in offspring of rats administered nateglinide at 1000 mg/kg (approximately 60 times the human therapeutic exposure with a recommended Starlix dose of 120 mg, three times daily before meals). It is not known whether Starlix is excreted in human milk. Because many drugs are excreted in human milk, Starlix should not be administered to a nursing woman.

Pediatric Use

The safety and effectiveness of Starlix in pediatric patients have not been established.

Geriatric Use

No differences were observed in safety or efficacy of Starlix between patients age 65 and over, and those under age 65. However, greater sensitivity of some older individuals to Starlix therapy cannot be ruled out.

ADVERSE REACTIONS

In clinical trials, approximately 2,600 patients with Type 2 diabetes were treated with Starlix. Of these, approximately 1,335 patients were treated for 6 months or longer and approximately 190 patients for one year or longer.

Hypoglycemia was relatively uncommon in all treatment arms of the clinical trials. Only 0.3% of Starlix patients discontinued due to hypoglycemia. Gastrointestinal symptoms, especially diarrhea and nausea, were no more common in patients using the combination of Starlix and metformin than in patients receiving metformin alone. Likewise, peripheral edema was no more common in patients using the combination of Starlix and rosiglitazone than in patients receiving rosiglitazone alone. The following table lists events that occurred more frequently in Starlix patients than placebo patients in controlled clinical trials.

Common Adverse Events (≥ 2% in Starlix patients) in Starlix Monotherapy Trials (% of patients)

	Placebo N=458	*Starlix* N=1441
Preferred term		
Upper Respiratory Infection	*8.1*	*10.5*
Back pain	*3.7*	*4.0*
Flu Symptoms	*2.6*	*3.6*
Dizziness	*2.2*	*3.6*
Arthropathy	*2.2*	*3.3*
Diarrhea	*3.1*	*3.2*
Accidental Trauma	*1.7*	*2.9*
Bronchitis	*2.6*	*2.7*
Coughing	*2.2*	*2.4*
Hypoglycemia	*0.4*	*2.4*

During postmarketing experience rare cases of hypersensitivity reactions such as rash, itching and urticaria have been reported.

Laboratory Abnormalities

Uric acid: There were increases in mean uric acid levels for patients treated with Starlix alone, Starlix in combination with metformin, metformin alone, and glyburide alone. The respective differences from placebo were 0.29 mg/dL, 0.45 mg/dL, 0.28 mg/dL, and 0.19 mg/dL. The clinical significance of these findings is unknown.

OVERDOSAGE

In a clinical study in patients with Type 2 diabetes, Starlix® (nateglinide) was administered in increasing doses up to 720 mg a day for 7 days and there were no clinically significant adverse events reported. There have been no instances of overdose with Starlix in clinical trials. However, an overdose may result in an exaggerated glucose-lowering effect with the development of hypoglycemic symptoms. Hypoglycemic symptoms without loss of consciousness or neurological findings should be treated with oral glucose and adjustments in dosage and/or meal patterns. Severe hypoglycemic

reactions with coma, seizure, or other neurological symptoms should be treated with intravenous glucose. As nateglinide is highly protein bound, dialysis is not an efficient means of removing it from the blood.

DOSAGE AND ADMINISTRATION

Starlix® (nateglinide) should be taken 1 to 30 minutes prior to meals.

Monotherapy and Combination with metformin or a thiazolidinedione

The recommended starting and maintenance dose of Starlix, alone or in combination with metformin or a thiazolidinedione, is 120 mg three times daily before meals.

The 60 mg dose of Starlix, either alone or in combination with metformin or a thiazolidinedione, may be used in patients who are near goal HbA_{1C} when treatment is initiated.

Dosage in geriatric patients

No special dose adjustments are usually necessary. However, greater sensitivity of some individuals to Starlix therapy cannot be ruled out.

Dosage in renal and hepatic impairment

No dosage adjustment is necessary in patients with mild-to-severe renal insufficiency or in patients with mild hepatic insufficiency. Dosing of patients with moderate-to-severe hepatic dysfunction has not been studied. Therefore, Starlix should be used with caution in patients with moderate-to-severe liver disease (See PRECAUTIONS, Hepatic Impairment).

HOW SUPPLIED

Starlix® (nateglinide) Tablets, 60 mg

Pink, round, beveled edge tablet with "STARLIX" debossed on one side and "60" on the other.

Bottles of 100..... NDC 0078-0351-05

Bottles of 500..... NDC 0078-0351-08

Starlix Tablets, 120 mg

Yellow, ovaloid, tablet with "STARLIX" debossed on one side and "120" on the other.

Bottles of 100..... NDC 0078-0352-05

Bottles of 500..... NDC 0078-0352-08

Storage

Store at 25° C (77° F); excursions permitted to 15° C -30° C (59° F -86° F).

Dispense in a tight container, USP.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 21-204/S-006

MEDICAL REVIEW(s)

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center For Drug Evaluation and Research

DATE: October 20, 2003

FROM: David G. Orloff, M.D.
Director, Division of Metabolic and Endocrine Drug Products

TO: NDA 21-204/S-006
Combination therapy with TZD

SUBJECT: NDA review issues and recommended action

Background
This application proposes a new indication for Starlix for use in combination with TZDs. The data supporting the new indication come from a single, multicenter, blinded, randomized trial. Patients treated with rosiglitazone 8 mg daily for 12 weeks (many discontinued from previous therapies) were randomized to placebo or Starlix and treated for an additional 12 weeks. Change from randomization in HbA1c was the primary endpoint.

Clinical safety and efficacy
The mean, placebo-subtracted effect on HbA1c of Starlix was 0.77 percentage units. This was statistically significant and is accepted as clinically significant as well. Because of the known highly variable efficacy of TZDs (indeed, up to 50% of patients have little to no response), an analysis was performed of the effect of Starlix by tertiles according to change from week -4 to week 0 on rosiglitazone alone. This analysis established that the effect of Starlix was consistent regardless of apparent response or non-response to RSG. Thus, Starlix is established as effective in combination with RSG. There were no new safety issues arising in this development program.

Labeling
Labeling has been negotiated with clear statements about the use of Starlix in addition to but not as a substitute for TZD in patients who have responded to TZD but are still not at glycemic therapeutic goal. In addition, at the request of OCPB, the Precautions and Clinical Pharmacology sections have been revised by deletion and insertion, respectively, of the same information on non-clinically significant results of drug interaction studies with Starlix.

Financial disclosure
The financial disclosure information is in order.
Recommendation
Approve

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/s/

David Orloff
10/20/03 05:04:36 PM
MEDICAL OFFICER

MEDICAL OFFICER REVIEW

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

APPLICATION #:	21204	APPLICATION TYPE:	sNDA.....
SPONSOR:	Novartis	PROPRIETARY NAME:	Nateglinide.....
CATEGORY OF DRUG:	Antidiabetic	USAN / Established Name:	Starlix.....
		ROUTE:	Oral..... .....
MEDICAL REVIEWER:	Robert I Misbin..	REVIEW DATE:	Feb 12, 2003.....

SUBMISSIONS REVIEWED IN THIS DOCUMENT

Document Date:	CDER Stamp Date:	Submission Type:	Comments:
Dec 19, 2002	Dec 26, 2002		

FILING MEMO

Signed: Medical Reviewer: Robert I Misbin MD Date: February 12, 2003

Medical Team Leader: _____ Date: _____

21204 Filing Memo

The NDA can be filed.

No advisory committee meeting is needed.

No inspections are recommended at present

Review issue:

For communication to Sponsor:

For two medications to be used together, there should be evidence that each one contributes to the efficacy of the combination. Study 2301 was a two-arm trial that compared nateglinide to placebo in patients who had not responded adequately to rosiglitazone. Nateglinide + rosiglitazone was better than rosiglitazone alone. But it is not clear from this study what rosiglitazone contributed to the efficacy of the nateglinide + rosiglitazone combination. It would be helpful to submit efficacy data that may have been obtained during the rosiglitazone-only pretreatment.

Robert I Misbin MD
February 12, 2003

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/s/

Robert Misbin
2/12/03 04:11:10 PM
MEDICAL OFFICER

David Orloff
2/12/03 07:01:05 PM
MEDICAL OFFICER

MEDICAL OFFICER REVIEW

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

APPLICATION #:	**21204**	**APPLICATION TYPE:**	**sNDA.....**
SPONSOR:	**Novartis**	**PROPRIETARY NAME:**	**Nateglinide.....**
CATEGORY OF DRUG:	**Antidiabetic**	**USAN / Established Name:**	**Starlix.....**
		ROUTE:	**Oral.....** **.....**
MEDICAL REVIEWER:	**Robert I Misbin..**	**REVIEW DATE:**	***10/16/03*****.....**

SUBMISSIONS REVIEWED IN THIS DOCUMENT

Document Date:	**CDER Stamp Date:**	**Submission Type:**	**Comments:**
Dec 19, 2002	**Dec 26, 2002**		
July 24, 2003		**Response to question**	

Recommended action: This application is approvable. Approval will require changes in labeling.

Because rosiglitazone and nateglinide work by different mechanisms, it is likely that their efficacies would be additive when used in combination. But because of flaws in trial design, the data submitted in this application should not be accepted at face value. The combination of Starlix with a thiazolidinedione may be approvable with the following language in the indications section:

Signed: **Medical Reviewer: Robert I Misbin MD** **Date: October 16, 2003**

Medical Team Leader: _____ **Date: _____**

Table of Contents: 2

Executive Summary:

1. Recommendations:

Because rosiglitazone and nateglinide work by different mechanisms, it is likely that their efficacies would be additive when used in combination. But because of flaws in the design of the trial, the data submitted in this appli
value. FDA has recognized that nateglinide is les
agents and has labeled Starlix accordingly. The c
thiazolidinedione indication should not be grante

This was done but not via the exact language below

In lieu of a new study, the Sponsor should limit its
who appear to have responded initially to rosiglitazone. The indication of nateglinide plus a thiazolidinedione may be approvable with the following language:

~~[redacted]~~

2. Summary of Clinical Findings

Study 2301 was a two-arm, 24 week trial that compared nateglinide to placebo in patients who had not responded adequately to rosiglitazone.

Efficacy results for the ITT population are shown below:

HbA1 in ITT population:

Treatment	N	Baseline mean	Adjust change	Diff
NAT + RSG	194	8.31	-0.71	-0.74
Placebo+ RSG	191	8.36	+0.03	

NAT=nateglinide
RSG=rosiglitazone

Nateglinide + rosiglitazone was better than rosiglitazone alone. But it is not clear from this study what rosiglitazone contributed to the efficacy of the nateglinide + rosiglitazone combination. The inclusion criteria in study 2301 specifically selected patients who had not responded "adequately". It therefore appears likely that many of the patients had not responded to rosiglitazone. This would mean that the results shown above were largely reflect, in essence, monotherapy with nateglinide.

This two-arm trial performed by Novartis is very different from add-on trials performed by other Sponsors. This trial is inadequate to show the effectiveness of the combination

of nateglinide + rosiglitazone unless it were shown that patients had initially responded to RSG.
Clinical Review

I Introduction and Background

Nateglinide (NAT) is a short acting insulin secretagog that is approved to be used for treatment of type 2 diabetes under the trader name Starlix. It is approved both as monotherapy and in combination with metformin. It is less effective than sulfonylureas in lowering HbA1c.

This sNDA requests labeling for Nateglinide to be used in combination with thiazolidinediones (TZD's). Results of one study were submitted. This was a placebo-controlled study of NAT in patients who had achieved inadequate glycemic control on monotherapy with rosiglitazone.

II No new issues relating to chemistry or toxicology

The statistical review, performed by Joy Mele, Division of Biometrics is particularly important and is discussed in a later section.

III No new issues relating to Pharmacokinetics or Pharmacodynamics

IV The application contains data from one controlled clinical trials..

V The review was conducted of the hard copy of the NDA. No routine inspections of the sites were performed.

The protocol requires that patients be on a background of rosiglitazone. Although rosiglitazone is approved as monotherapy, its efficacy is unpredictable. The widest use of rosiglitazone is in combination with other drugs. Its use as monotherapy is very much less than metformin and sulfonylureas. It is reasonable to assume that most patients who participated in this study were withdrawn from other treatments and placed on rosiglitazone in order to make them eligible. This is recognized in the consent document with the following statement:

Most patients will enter a 3-month pre-study period. If you agree to take part in this study, you will be asked to stop taking the antidiabetic medication you now take. During the three months pre-study period you will take rosiglitazone 8 mg once daily...etc.."

The consent document states goes on to state under "alternative /previous treatment":

Other medications are available to treat diabetes. If you have questions about other therapies such as Diabetes, Micronase, Glucophage and Glucotrol, as well as diet, ask Dr..... for additional information. However, if you are already on such a treatment, it

will be withdrawn 3 months prior to the official study entry and during the course of the study. Your study doctor will inform you of the risk associated with the withdrawal"

Having reviewed the consent documents, I cannot find evidence that patients were informed of the deterioration in glucose control that frequently occurs when rosiglitazone is substituted for other antidiabetic medications. I believe this is a serious defect in the consent document.

On the other hand, I am not able to document a group of patients in whom substantial deterioration occurred. Even for the subset who did not show a decrease in HbA1c from week –4 to baseline (see statistical report), the mean HbA1c at baseline was about 8.5% and fell thereafter. Patients whose HbA1c rose substantially during the three month pre-study period may have been culled out and not randomized. Although I am unhappy with the consent document and withdrawal of medication during the "3-month pre-study", do not feel there is a strong enough case to recommend that the study be rejected on ethical grounds.

V1 Review of Efficacy

This was a 24 week double blind placebo controlled study in patients with type 2 diabetes whose hyperglycemia had been inadequately controlled on rosiglitazone (RSG).

Patients were to have been on 8 mg per day of RSG for at least 12 week prior to screening at week –4 and have HbA1c 7% to 11% with FPG 110-240 mg/dl (6.1-13.3mM) at week –4. There was a 4 week run-in. Patients who still met the glycemic inclusion criteria were randomized to RSG 8 mg od plus Nateglinide 120 tid before meals or RSG 8 mg plus Nateglinide placebo. RSG was given once daily with breakfast.

The randomized population had a mean age of 57 years, 59% male, 91kg, BMI of 31.1, 79% Caucasian and 14% black. The NAT group was 44% female compared to the placebo group was 38% female.

Results:

The changes in HbA1c, FPG and 2-hr post-meal challenge glucose for the ITT population, baseline to endpoint, follow in the table. There is an ANCOVA adjustment using investigative site, and baseline. The difference between NAT and placebo was significant in all cases.

HbA1 in ITT population:

Treatment	N	Baseline mean	Adjust change	Diff
NAT + RSG	194	8.31	-0.71	-0.74
Placebo+ RSG	191	8.36	+0.03	

NAT=nateglinide
RSG=rosiglitazone

The Sponsor states that the greater reduction in HbA1c with NAT was observed in all sub-sets.

Changes in fasting and two-hour post meal glucose are shown below:

FPG (mM) in ITT population:

Treatment	N	Baseline mean	Adjust change	Diff
NAT + RSG	197	9.79	-0.62	-0.76
Placebo+ RSG	197	9.97	+0.14	

2 hour post meal glucose, mM

Treatment	N	Baseline mean	Adjust change	Diff
NAT + RSG	159	13.95	-2.75	-3.10
Placebo+ RSG	155	14.42	+0.35	

Fasting insulin concentrations were similar in both treatment groups. However, postprandial insulin and C peptide were significantly increased by NAT.

As shown in the table below, change in body weight was greater with NAT than with placebo. There were no significant differences in changes in serum lipids between the two groups.

Body weight, kg

Treatment	N	Baseline mean	Adjust change	Diff
NAT + RSG	194	92.	3	2
Placebo+ RSG	191	90	1	

Critique:

Concomitant medications

As shown in the table, 8 NAT+RSG and 5 RSG+placebo patients took the following prohibited drugs during the randomized period:

	Nat + RSG	RSG
Metformin –	3	1
Metformin+sulfonylurea		1
Phentermine	1	
Insulin	2	3
Orlistat	2	

The Sponsor was requested to recalculate the efficacy data excluding these patients.

As shown by the results in the following table, use of these medications dies not appear to impact the efficacy results.

	Total		Excluding other medications	
	NAT+RSG	RSG+plcbo	NAT+RSG	RSG+plcbo
N=	194	191	186	185
Baseline HbA1c	8.31	8.36	8.28	8.35
Change	-0.71	+0.03	-0.75	+0.02
Difference	**-0.74**		**-0.77**	

2 **Unstable baseline**

The Sponsor defined the baseline HbA1c as the average of the two values obtained at –2 and zero. However, review of the data from the individual time points (see table) reveals that the HbA1c values continued to decline during the run-in. Particularly in the RSG+ Nateglinide arm, the HbA1c showed no sign of stabilizing, and was approximate – 0.067% units/week for the entire run-in. The change during the controlled portion was only –0.033. Strictly speaking, this means that all of the efficacy attributed to Nateglinide could be accounted for by the declining baseline observed before treatment with nateglinide began. However additional statistical analysis by Joy Mele (p 11) showed that changes in HbA1c during the run-in did not appear to effect efficacy.

Run-in	RSG + Nateglinide arm	RSG + placebo arm
Week - 4	8.52	8.48
Week -2	8.37	8.35
Week 0	8.25	8.32
Change	-0.27	-0.16
Change per week	-0.067/week	-0.040
Controlled trial		
Week 16	7.40	8.32
Week 24	7.45	8.16
Change (0-24)	-0.80	-0.16
Change per week	-0.033/week	-0.007/week

Trial Design

For two medications to be used together, there should be evidence that each one contributes to the efficacy of the combination. Study 2301 was a two-arm trial that compared nateglinide to placebo in patients who had not responded adequately to rosiglitazone. Nateglinide + rosiglitazone was better than rosiglitazone alone. But it is not clear from this study what rosiglitazone contributed to the efficacy of the nateglinide + rosiglitazone combination. . The inclusion criteria in study 2301 specifically selected patients who had not responded "adequately" to RSG.

But there was no assurance that the patients selected for this trial had responded to RSG at all. The two arm trial performed by Novartis is inadequate to show that the effectiveness of the combination of RSG plus nateglinide unless it were shown that patients had initially responded to RSG.

Indeed, Novartis itself used a three-arm trial in its original NDA for the approval of Nateglinide plus metformin.

Although not specifically broken down by dosing regimen and indication, the response to rosiglitazone is consistently lower in males than females. In the current sNDA for Starlix plus RSG, 59% of patients were male.

** For simplicity, I use the term "three arm trial" to mean a trial designed to compare each monotherapy to the combination. Some of the examples cited had more than three arms because of multiple doses of test drug.

Comments on Additional Statistical Analysis:

In an attempt to remedy the flaws in trial design, Joy Mele performed an efficacy analysis based on the change in HbA1c during the run-in. Shown below are data for the three tertiles (-0.4% units, -0.4 to –0.1% units, -0.1 and above). The patients who experienced a decline of at least 0.4% units in HbA1c from week –4 to baseline can reasonably be considered "RSG-responders" because most of these patients had probably been started on RSG at week –12. There were 67 patients (33 M and 34F) in the NAT +RSG arm and 54 patients (33M and 21F) in the placebo+RSG arm. The mean placebo-subtracted reduction in HbA1c was 0.77% units. Mean weight change in +3.4 kg vs +1.4 kg.

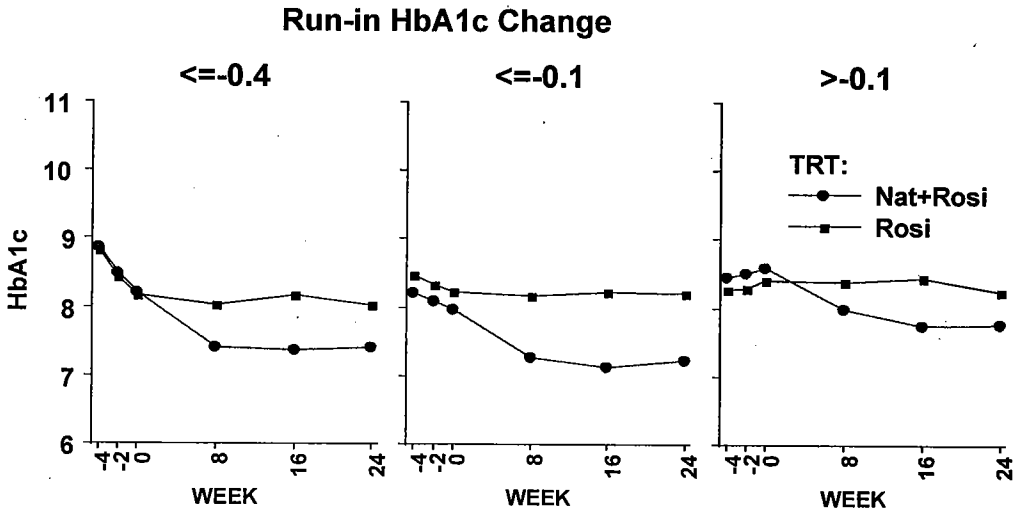

Table 5. Results during run-in

	Nat+Rosi (n=194) Mean (SD)	Rosi (n=191) Mean (SD)	p-value
HbA_{1c} (%)			
Week –4	8.51 (0.9)	8.49 (1.0)	ns
Week –2	8.37 (0.9)	8.36 (1.0)	ns
Week 0	8.25 (0.9)	8.33 (1.0)	ns
Change from –4 to 0	-0.27 (0.4) (N=184)	-0.20 (0.4) (N=183)	.05
Change from –2 to 0	-0.11 (0.2) (N=192)	-0.06 (0.3) (N=182)	.02 within grp change NS
Baseline (mean of –2 and 0)	8.3 (0.9)	8.4 (1.0)	ns
HbA_{1c} (%) by Run-in Change Tertiles			Trt diff
Run-in ch<=-0.4	-0.96 (n=67)	-0.19 (n=54)	0.77
Run-in ch >-0.4 and <=-0.1	-0.70 (n=59)	+0.07 (n=51)	0.77
Run-in ch >-0.1	-0.61 (n=58)	+0.04 (n=78)	0.65 all p<.0002

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VII Safety

Summary of safety:

There were no deaths. 9/200 patients on NAT +RSG had at least one hypoglycemic event compared to no patients on Placebo + RSG. However, none of these hypoglycemic events required assistance led to discontinuation or had plasma glucose < 2.2 mM. There were small decreases in hemogram values in both arms, presumable due to RSG. One patient on combination therapy had an ALT value of 211 U/L at endpoint, which the investigator thought "was not clinically significant".

VIII. Dosing regimen, labeling and administrative issues -

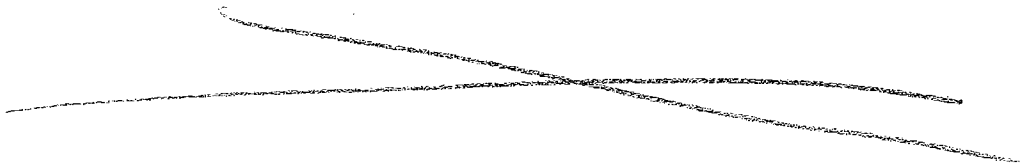
Labeling

Indications:

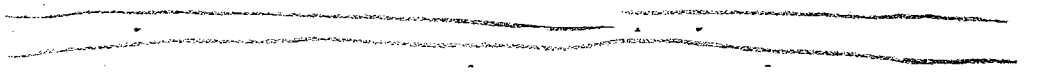
The current label states:

Starlix is also indicated for use in combination with metformin. In patients whose hyperglycemia is inadequately controlled with metformin, Starlix may be added to but not substituted for metformin.

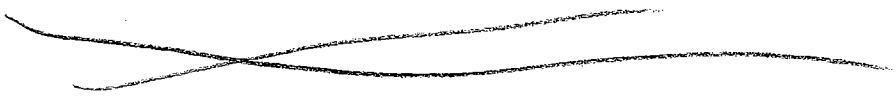
The Sponsor proposes the following revision (in bold)



In contrast to the language about metformin



The following wording would be preferable:



IX Use in special populations: No change to existing the label is needed.

X Conclusion and Recommendations

Nateglinide is an insulin secretagog. Rosiglitazone is an insulin sensitizer. Rosiglitazone is already approved for use in combination with other insulin secretagogs (sulfonylureas and repaglinide) and with insulin itself. Because rosiglitazone and nateglinide work by different mechanisms, it is likely that their efficacies would be additive when used in combination.

The use of TZD's, including, rosiglitazone as monotherapy is problematic. Approximately one half of patients experience a reduction in HbA1c of a similar magnitude (1-2% units) as what one would expect from a SFU, repaglinide or metformin. But nearly one half fail to respond.* Although starting a drug-naïve patient on rosiglitazone may be "hit or miss", the benefit is likely to be long-lasting response in those patients who respond initially. For this reason, I think it is good medical practice to start patients on rosiglitazone with the plan to discontinue treatment in patients who fail to respond by 2 months. **To treat patients with rosiglitazone in the absence of a demonstrable response would expose patients to the potential harm of the drug without likelihood of benefit. But this result is what would ensue from approval of this application.**

The problem of patients who do not respond to monotherapy with pioglitazone is similar to the problem of non-responders to RSG. Satoh et al (Diabetes care 26:2493, 2003) classified patients as responders or non-responders to 45 mg of pioglitazone for three months based on HbA1c reduction of greater or less than 1%. The 57% responders had a mean HbA1c reduction of 1.5% (8.3% to 6.8%). The 43% non-responders had a mean HbA1c change 0.1% (7.8% to 7.7%. These results illustrate the "all or none" responses characteristic of TZD's as monotherapy.

FDA has recognized that nateglinide is less effective than other oral antidiabetic agents and has labeled Starlix accordingly. The combination with thiazolidinedione indication should not be granted until additional information is provided and the label is revised. Ideally, a new trial should be performed that could be considered adequate and well-controlled. A discussion of potential trial designs follows in a later section.

As an alternative to a new trial, the combination indication could be supported by data from the subset of patients who responded to rosiglitazone (See **Comments on Additional Statistical Analysis** p11). The application is approvable based on analysis of data from this subset, provided that the Sponsor revises the label as indicated below:

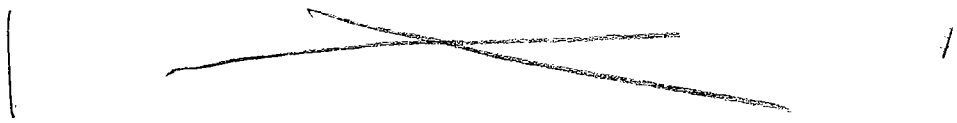
1

2 Indications and Usage Section:

Paragraph 1 – no change

Paragraph 2 –

Paragraph 3 should state:



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Trial design for combination therapy:

The most straight forward trial design is a three arm comparisons of the combination of NAT+RSG vs monotherapy with NAT or RSG alone. Naïve patients or patients inadequately controlled on any monotherapy would be eligible.

Thus switching a patients from a SFU or metformin to NAT would almost certainly result in deterioration of glycemic control.

An alternative design would be a comparison of RSG vs placebo in patients inadequately controlled on monotherapy with NAT.

The alternative that I favor is a controlled comparison of Nateglinide plus rosiglitazone vs Nateglinide monotherapy and rosiglitazone monotherapies using a controlled withdrawal. A brief description follows:

A controlled comparison of Nateglinide plus rosiglitazone to Nateglinide monotherapy and rosiglitazone monotherapy in patients who had been treated with a combination of Nateglinide plus rosiglitazone.

Eligible patients will have been on a combination of Nateglinide plus rosiglitazone for at least four months and have HbA1c <8 %. In order to aid recruitment, the Sponsor may wish to include patients who had been on any insulin secretagog (SFU, repaglinide or nateglinide) plus any TZD. Patients should be treated with a one month run-in of Nateglinide 120 mg tid plus rosiglitazone 8 mg qd. Those whose HbA1c is < 8% at baseline, and did not change by more than +/- 0.3% units from screening to baseline can

be randomized to Nateglinide 120 mg tid plus Rosiglitazone 8 mg, or Nateglinide 120 mg tid, or Rosiglitazone 8 mg monotherapy. The controlled portion should last at least three months and can be either open-label or "double dummy". The primary measure of efficacy is change in HbA1c from baseline to endpoint. The study should have the power to detect superiority of the combination of Nateglinide plus Rosiglitazone to each of the monotherapies.

Approval would require that rise in HbA1c was less with NAT+RSG than with either NAT or RSG alone. This approach would be sensitive to the potential problem of RSG unresponsiveness. If patients on NAT+RSG were not responding to the RSG component, the following result would occur:

Rise in HbA1c on RSG would be greater than in the other two arms

And

Change in HbA1c on NAT+ RSG **would equal** change in NAT alone

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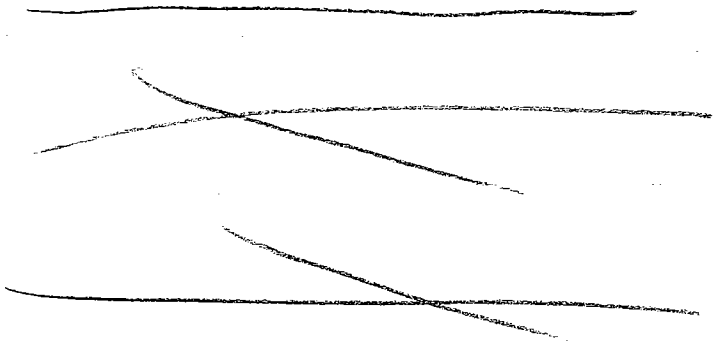
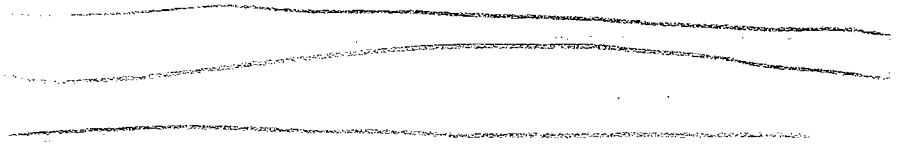
1 

2 Indications and Usage Section:

Paragraph 1 – no change

Paragraph 2 –

Paragraph 3 should state:



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/s/

Robert Misbin
10/16/03 05:25:41 PM
MEDICAL OFFICER

David Orloff
10/16/03 06:32:50 PM
MEDICAL OFFICER
concur with AP pending final labeling

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 21-204/S-006

CHEMISTRY REVIEW(S)

CHEMIST'S REVIEW

1. Organization CDER/HFD-510 Division of Metabolism and Endocrine Drug Products	**2. NDA # 21-204** Approved: 22-DEC-2000
3. Name and Address of Applicant: Novartis Pharmaceutical Corporation	**4. Supplement** SE1-006 Doc. 19-DEC-2002
	5. Name Of The Drug Starlix® Tablets
	6. Nonproprietary Name Nateglinide
7. Supplement provides support of an expanded indication for use in combination with antidiabetic drugs in the thiazolidinedione class.	**8. Amendment** --

9. Pharmacological Category Hypoglycemic Agent. Adjunct to diet to improve glycemic control in patients with NIDDM.	**10. How Dispensed** Oral Rx	**11. Related** --
12. Dosage Form Tablets	**13. Strength(s)** 60-, 120- and 180-mg	

14. **Chemical Name and Structure**
Nateglinide
$C_{19}H_{27}NO_3$
MW = 317,43
CAS registry #: 105816-04-4

15. Comments: This Prior Approval Supplement provides support of an expanded indication for use in combination with antidiabetic drugs in the thiazolidinedione class. Currently, Starlix® is approved for use alone or in combination with metformin, to control blood glucose, in patients with type 2 diabetes mellitus. In support of the proposed expanded indication the applicants provides: (1) clinical data, including results of a well-controlled, clinical safe and efficacy trial, (2) human pharmacokinetics and bioavailability information, including data from two drug interaction studies relevant to the expanded indication, and (3) current and proposed labeling. As stated in the cover letter, after taking into account the "increased of use" (as defined in 21 CFR §25.5(b)4) of the active moiety nateglinide, the estimated concentration of the drug substance at the point of entry into the aquatic environment will be less than 1 part per billion (ppb). To the best of Novartis' knowledge, no extraordinary circumstances exist which may significantly effect the quality of the human environment and would require the preparation of an Environmental Assessment. As set forth in 21 CFR §25.31(b) this *submission is categorically excluded from the requirement to prepare an Environmental Assessment or an Environmental Impact Statement.*

16. Conclusions and Recommendations: Efficacy supplement. Both drug substance and drug product remained unchanged. The estimated concentration of the drug substance at the point of entry into the aquatic environment, taking into account the "increased use", will be less than 1 part per billion (ppb). From the CMC point of view, this supplement can be approved.

17. Reviewer Name (and signature) **Date Completed:** 24-SEP-2003

Xavier Ysern, PhD

R/D Init.
Stephen Moore, PhD
Chemist Team Leader

filename: /nda/21204s06.doc

PA-Suppl

AP

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/s/

Xavier Ysern
9/29/03 08:48:53 AM
CHEMIST

Stephen Moore
9/29/03 09:34:45 AM
CHEMIST

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 21-204/S-006

STATISTICAL REVIEW(S)

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Pharmacoepidemiology and Statistical Science
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA/Serial Number:	21-204/S-006 SE1
Drug Name:	Starlix (nateglinide tablets)
Indication(s):	Treatment of Type 2 Diabetes
Applicant:	Novartis
Date(s):	Submitted 1/20/03, PDUFA goal date 10/20/03
Review Priority:	Standard
Biometrics Division:	Division of Biometrics 2 (HFD-715)
Statistical Reviewer:	Joy Mele, M.S.
Concurring Reviewers:	Todd Sahlroot, Ph.D.
Medical Division:	Division of Metabolic and Endocrine Drug Products (HFD-510)
Clinical Team:	Robert Misbin, M.D. (HFD-510)
Project Manager:	Jena Weber (HFD-510)

Keywords: NDA review, clinical studies, add-on therapy

1. EXECUTIVE SUMMARY OF STATISTICAL FINDINGS

1.1 Conclusions and Recommendations

The single trial (Trial A2301) submitted by the sponsor demonstrated significant decreases in HbA_{1c} due to the addition of nateglinide therapy (120 mg) in patients considered to be inadequately controlled on rosiglitazone alone (8 mg OD). This single trial was an add-on trial with two treatment arms (nateglinide plus rosiglitazone and rosiglitazone alone) making these trial results applicable only to patients inadequately treated with rosiglitazone. So there is no evidence provided that combination therapy in naïve patients is advantageous over monotherapy with rosiglitazone or nateglinide alone.

Statistical analyses of the data from Trial A2301 led to the following conclusions:

- The addition of nateglinide to rosiglitazone resulted in a statistically significant mean HbA_{1c} treatment effect of -0.74%
- Subgroup analyses showed consistent treatment effects regardless of age, gender, baseline HbA_{1c} , run-in change in HbA_{1c} and duration of diabetes
- Significant weight gains were seen in the combination group compared to the monotherapy group with 81% of the patients showing a weight gain at endpoint; 34% gained more than 4 kg.

1.2 Brief Overview of Clinical Studies

The results of one clinical trial (Trial 2301) were submitted to support an indication for combination therapy of rosiglitazone (8 mg) plus nateglinide (120 mg) in patients inadequately treated with rosiglitazone alone. A brief overview of this trial is given in Table 1.

Table 1. Clinical Trials

Study (# of centers)	Design	Treatment groups (N)	Duration of treatment
2301 (82 USA centers)	Double-blind, randomized, parallel, controlled, add-on	Rosiglitazone 8 mg plus nateglinide 120 mg (200) Rosiglitazone 8 mg (202)	4-week run-in of rosiglitazone; 24 weeks of randomized treatment

2. Data Sources

The NDA application was submitted both as paper volumes and electronically. For the statistical review, volumes 1 and 15 through 20 were reviewed. Data for analysis was accessed from the CDER Electronic Document Room at \\CDSESUB1\N21204\S_006\2002-12-19.

All tables and figures in this review were created by this statistical reviewer. Results were computed by the reviewer unless otherwise noted.

3. Statistical Evaluation

3.1 Evaluation of Efficacy

Study A2301 (conducted 6/2000 to 7/2002)

Design

Study A2301 was a multicenter, double-blind, randomized clinical trial designed to assess the efficacy and safety of combination therapy of nateglinide and rosiglitazone in patients inadequately treated with rosiglitazone alone. Patients diagnosed with Type 2 diabetes for at least six months and who received rosiglitazone treatment for at least 3 months prior to screening were given rosiglitazone 8 mg for 4 weeks. After the run-in period, eligible patients were randomized to rosiglitazone 8 mg OD or rosiglitazone 8 mg OD plus nateglinide 120 mg and treated for 24 weeks.

Entry criteria at Week –4 included the following:

- Age 21 years or older and Type 2 diabetes for at least 6 months
- Rosiglitazone 8 mg for at least 3 months prior to Week -4
- No sulfonlyurea for at least 5 months prior to Week -4
- No oral antidiabetic medication except rosiglitazone for 3 months prior to Week -4
- FPG≤240 at Week -4 and Week -2

Entry criteria at baseline (Week 0) included the following:

- 7%≤HbA_{1c}≤11% mean of Weeks -4 and -2
- 110≤FPG≤240 at Week -4 and Week –2

HbA_{1c} was measured at Weeks -4, -2, 0, 8, 16 and 24. The primary efficacy endpoint is HbA_{1c} change from baseline at Week 24 or at the last observation. Baseline was computed as the average of Week -2 and 0. To compare groups, an analysis of covariance with baseline HbA_{1c} as the covariate was performed on data from an ITT population (all randomized patients with at least one response measurement on trial therapy).

Patient Disposition

A total of 634 patients were screened and entered the run-in period of rosiglitazone monotherapy. Of the 634, 402 were randomized to treatment; 200 to nateglinide and rosiglitazone and 202 to rosiglitazone alone (Table 2). The primary reason patients were not randomized was low HbA_{1c} during the run-on (about 40% of the 232 patients not randomized).

Table 2. Study A2301 Patient Disposition

	Nat+Rosi	Rosi	All
Screened			634
Randomized	200 (100%)	202 (100%)	402 (100%)
Wk 8 Wk 16 Wk 24	195 (98%) 185 (93%) 176 (88%)	194 (96%) 185 (92%) 168 (83%)	
Completers (Pts with Wk 24 data)	169 (85%)	158 (78%)	327 (81%)
ITT ITT with HbA_{1c} data	198 (99%) 194 (97%)	197 (98%) 191 (95%)	395 (98%)

More patients completed the 24 weeks of therapy on combination therapy (88%) than on rosiglitazone monotherapy (83%); about 5% of completers did not have data at their last visit.

The ITT population (the analysis population) consisted of 98% of the randomized patients with only 2 patients in the combination group and 5 patients in the monotherapy group not providing data.

The primary reason for discontinuation (Table 3) from the rosiglitazone monotherapy group was lack of efficacy (9%, about half occurred after about 4 months of therapy) and from the combination group, the primary discontinuation reason was patient request (5.5%). The adverse event rate was the same in both groups (4%).

Table 3. Study A2301 Reasons for discontinuation

	Nat+Rosi (n=200)	Rosi (n=202)
ADE	8 (4%)	8 (4%)
Pt request	11 (5.5%)	8 (4%)
Prot. Viol.	3 (1.5%)	1 (0.5%)
Lost-to-FU	3 (1.5%)	7 (3.5%)
Lack of efficacy	5 (2.5%)	19 (9%)
Other	1 (0.5%)	1 (0.5%)

Baseline Demographics

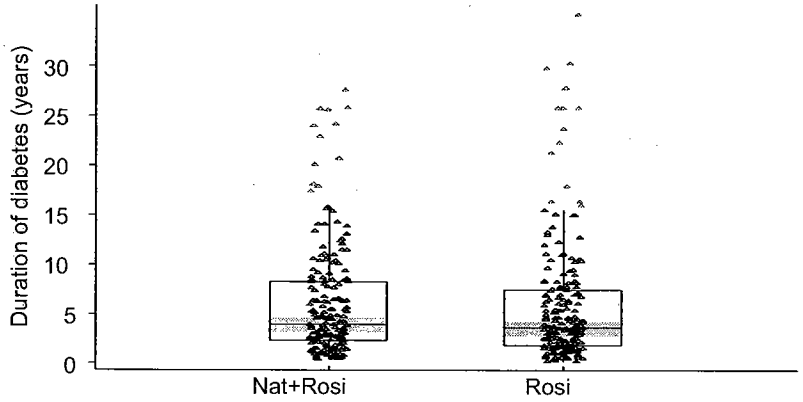
The treatment groups are comparable with respect to age, gender and race (Table 4). The mean age was 57 years; about ¼ of the patients were 65 years or older. The majority of the patients were males (about 60%). About 80% were Caucasian and about 15% Black.

Table 4. Study 2301 Patient Demographics for All Randomized Patients

	Nat+Rosi (n=200)	Rosi (n=202)
Age		
Mean (SD)	57 (11)	57 (12)
Range	28-83	26-83
%≥65years	22%	27%
Gender		
% female	44%	38%
Race		
% Caucasian	81%	77%
% Black	15%	14%
BMI		
Mean (SD)	32 (4)	31 (4)
%≥30 kg/m^2	63%	52%
Duration of Type 2 Diabetes (years)		
Mean (SD)	5.9 (5.6)	5.8 (6.2)
Median		
Range	0.4-28	0.2-35
Baseline Mean (SD)		
HbA_{1c} (%)	8.3 (0.9)	8.4 (1.0)
FPG (mmol/L)	9.8 (2.1)	10 (2.1)

The average time since diagnosis of Type 2 diabetes was about 6 years in both groups with a range of about 3 months to 35 years. Boxplots of the duration data show a small shift upwards in the combination group compared to the monotherapy group (Figure 1). The median for the combination group is 3.95 years and the median for the monotherapy group is 3.6 years; a statistically non-significant difference of about 4 months.

Figure 1. Boxplots of duration of diabetes (years) by treatment group



Baseline HbA_{1c} and baseline FPG were computed as the average of Weeks –2 and 0; the data

for those timepoints and for Week –4, as well, are depicted in the boxplots in Figures 2 and 3. The FPG data (Figure 3) shows essentially no change during the run-in while the HbA_{1c} plots (Figure 2) show a decrease overtime. The change in HbA_{1c} from Week –4 to 0 was statistically significant in each randomized group while the change from Week –2 to 0 was not. The latter suggests to this reviewer that averaging Week –2 and 0 to compute baseline is acceptable.

Figure 2. Boxplots of HbA_{1c} during the run-in period of rosiglitazone only by randomized treatment group

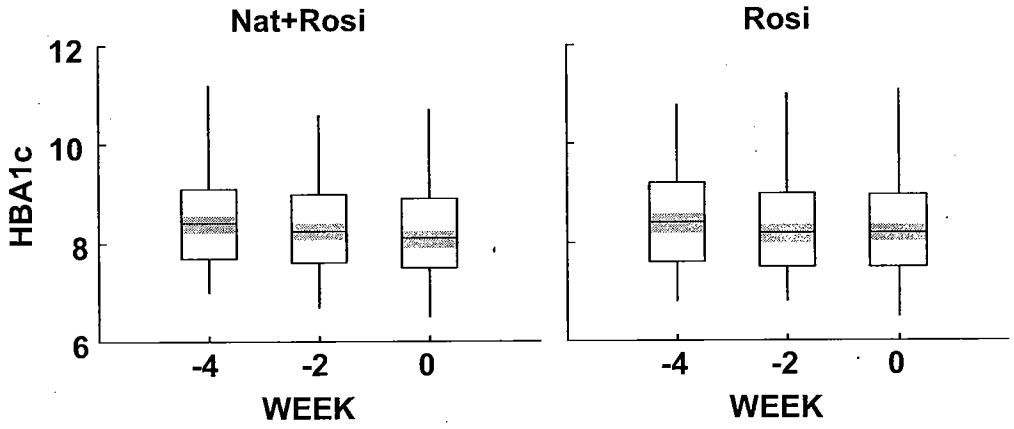
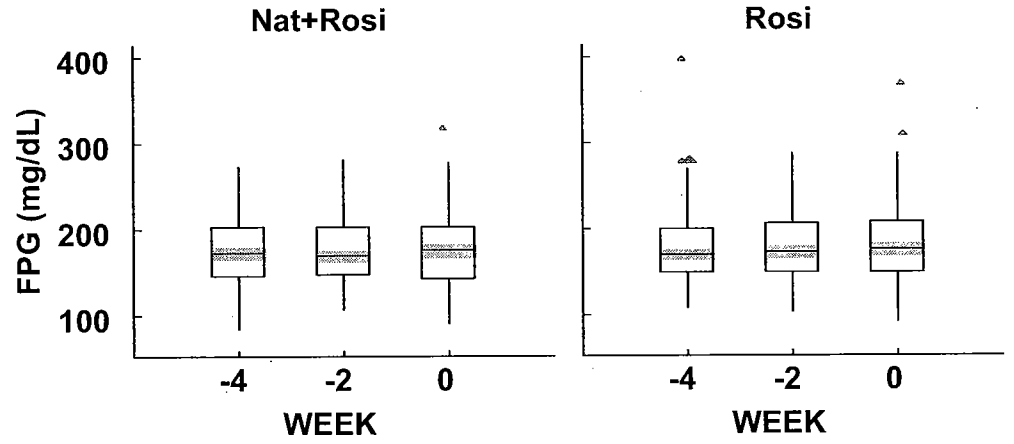


Figure 3. Boxplots of FPG during the run-in period of rosiglitazone only by randomized treatment group



About half the patients presented with hypertension. About 40% of the patients were using HMG CoA reductase inhibitors at baseline.

Efficacy Results

HbA_{1c}, FPG and 2-hour PPG Results

The addition of nateglinide to rosiglitazone resulted in highly statistically significant decreases in HbA_{1c} (primary endpoint) and FPG at Weeks 8, 16, 24 and 24 LOCF compared to rosiglitazone alone (Table 5). An ANCOVA model with baseline as a covariate yields a least squares mean treatment difference of –0.76% for HbA_{1c}.

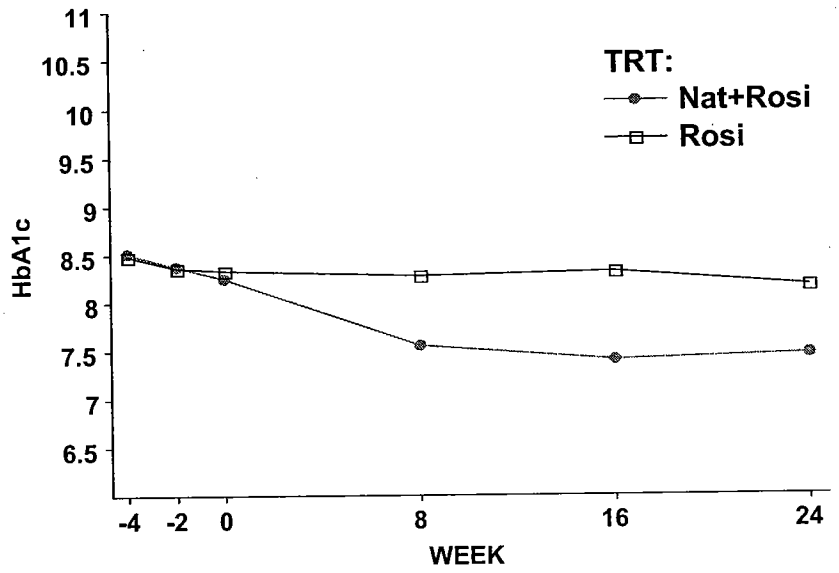
Table 5. Efficacy Results at each timepoint of the trial and at endpoint (LOCF)

	Nat+Rosi (n=194) Mean (SD)	Rosi (n=191) Mean (SD)	Treatment Difference LS Mean	p-value
HbA_{1c} (%)				
Baseline	8.3 (0.9)	8.4 (1.0)		NS
Week 8 Change	-0.75 (0.59)	-0.08 (0.62)	-0.66	<.0001
Week 16 Change	-0.87 (0.82)	0.00 (0.74)	-0.87	<.0001
Week 24 Change	-0.82 (0.86)	-0.08 (0.91)	-0.74	<.0001
Week 24 LOCF Change				
Mean (SD)	-0.77 (0.84)	-0.008 (0.90)		
LS Mean	-0.77	-0.007	-0.76	<.0001
FPG (mg/dL)				
Baseline	9.8 (2.1)	10 (2.1)		NS
Week 8 Change	-18.8 (30.6)	-2.4 (29.6)	-17.6	<.0001
Week 16 Change	-14.7 (31.0)	-5.7 (35.5)	-9.6	.006
Week 24 Change	-13.3 (31.7)	+0.8 (39.6)	-14.0	.0004
Week 24 LOCF Change				
Mean (SD)	-13.2 (30.5)	-0.3 (42.1)		
LS Mean	-13.6	+0.05	-13.6	.0002
2-hr PPG (mg/dL)	(n=159)	(n=155)		
Baseline	251.2 (69)	259.7 (66)		
Week 24 LOCF Change				
Mean (SD)	-45.9 (59)	+6.5 (61)		
LS Mean	-46.9	+7.5	-54.4	<.0001

Prandial plasma glucose was measured as a secondary endpoint. A standard meal challenge was performed at Week 0 and Week 24. A significant change from baseline in 2-hour post-prandial plasma glucose values at Week 24 LOCF were seen for the combination compared to rosiglitazone alone (Table 5).

Figure 4 depicts the mean HbA_{1c} at each timepoint of the trial from Week –4 to Week 24 for the observed cases data. Essentially no change is seen in HbA_{1c} in the group randomized to rosiglitazone monotherapy while in the combination group, the most significant decrease is seen by Week 8 with no appreciable drops in HbA_{1c} thereafter.

Figure 4 Mean HbA_{1c} at each timepoint by treatment group



Weight Gain Results

Weight gain was observed in both treatment groups with statistically significantly greater gains observed in the combination therapy group than the monotherapy group (treatment difference of 1.9 kg, p<.0001, Table 6). About 80% of the nateglinide plus rosiglitazone patients had a weight gain at endpoint compared to 59% of the rosiglitazone patients. These gains were not correlated with changes in HbA_{1c} (r^2<.01).

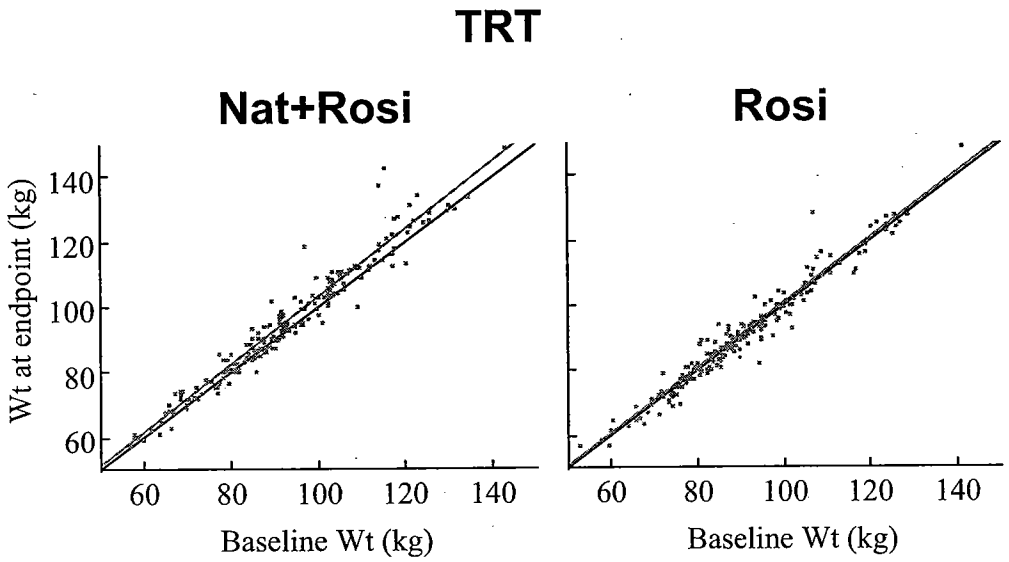
Table 6. Efficacy Results at each timepoint of the trial and at endpoint (LOCF)

	Nat+Rosi (n=194) Mean (SD)	Rosi (n=191) Mean (SD)	Treatment Difference LS Mean	p-value
Weight gain (kg)	(n=194)	(n=191)		
Baseline	92.2 (17)	90.3 (16)		
Week 24 LOCF Change				
Mean (SD)	+3.1 (4.3)	+1.1 (3.5)		
LS Mean	+3.0	+1.1	+1.9	<.0001
% of pts by weight gain				
≤ 0 kg	21%	41%	NA	<.0001 (CMH)
>0 to 2 kg	25%	27%		
>2 to 4 kg	20%	15%		
>4 to 8 kg	27%	14%		
> 8 kg	7%	4%		

Most of the weight gain in the combination group occurred during the first 4 months of therapy. Essentially no gain was seen during the run-in on rosiglitazone alone.

On average, in the combination group, more weight gain was observed for patients heavier at baseline (regardless of gender) (Figure 5).

Figure 5. Weight at endpoint by baseline weight for each treatment group. Fitted line and identity line are plotted.



3.2 Evaluation of Safety

See Dr. Misbin's medical review for an evaluation of safety.

4. Findings in Special/Subgroup Populations

4.1 Gender, Race and Age

Primary efficacy results by gender and for patients under 65 or 65 and older are shown below in Table 7; only 15% of the patients were non-Caucasian so no results by race are presented. The magnitude of the effects within each treatment group are larger for females than males; this is consistent with data for rosiglitazone where females generally exhibit a larger effect than males. However the treatment differences are essentially the same across gender so no gender differences are seen due to adding-on nateglinide.

Patients 65 years or older had HbA_{1c} results consistent with the overall results (Table 7).

Table 7. HbA_{1c} (%) Efficacy Results by gender and age at endpoint (LOCF)

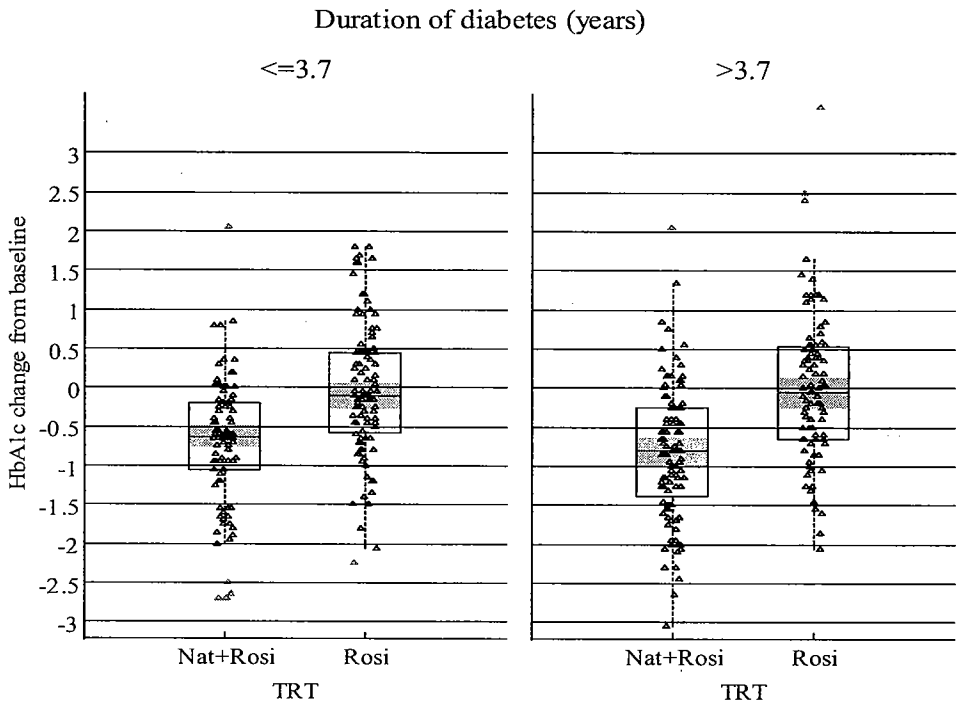
	Nat+Rosi Mean (SD)	Rosi Mean (SD)	Treatment Difference LS Mean	p-value
Gender				
Males	n=110	n=118		
Baseline	8.3 (0.9)	8.5 (0.9)		
Week 24 LOCF Change	-0.66 (0.9)	+0.05 (0.9)	-0.61	<.0001
Females	n=84	n=73		
Baseline	8.3 (0.9)	8.2 (1.0)		
Week 24 LOCF Change	-0.91 (0.8)	-0.10 (0.9)	-0.62	0.0001
Age				
<65 years	n=152	n=138		
Baseline	8.4 (0.9)	8.4 (0.9)		
Week 24 LOCF Change	-0.73 (0.9)	+0.08 (1.0)	-0.82	<.0001
≥65 years	n=42	n=53		
Baseline	8.1 (0.9)	8.2 (0.9)		
Week 24 LOCF Change	-0.89 (0.7)	-0.22 (0.7)	-0.57	0.01

4.2 Other Special/Subgroup Populations

4.2.1 Duration of diabetes

The distribution of HbA_{1c} results by median duration of diabetes shows similar treatment responses within each treatment group and between groups. Analyses adjusting for duration of diabetes yielded a treatment effect of –0.74.

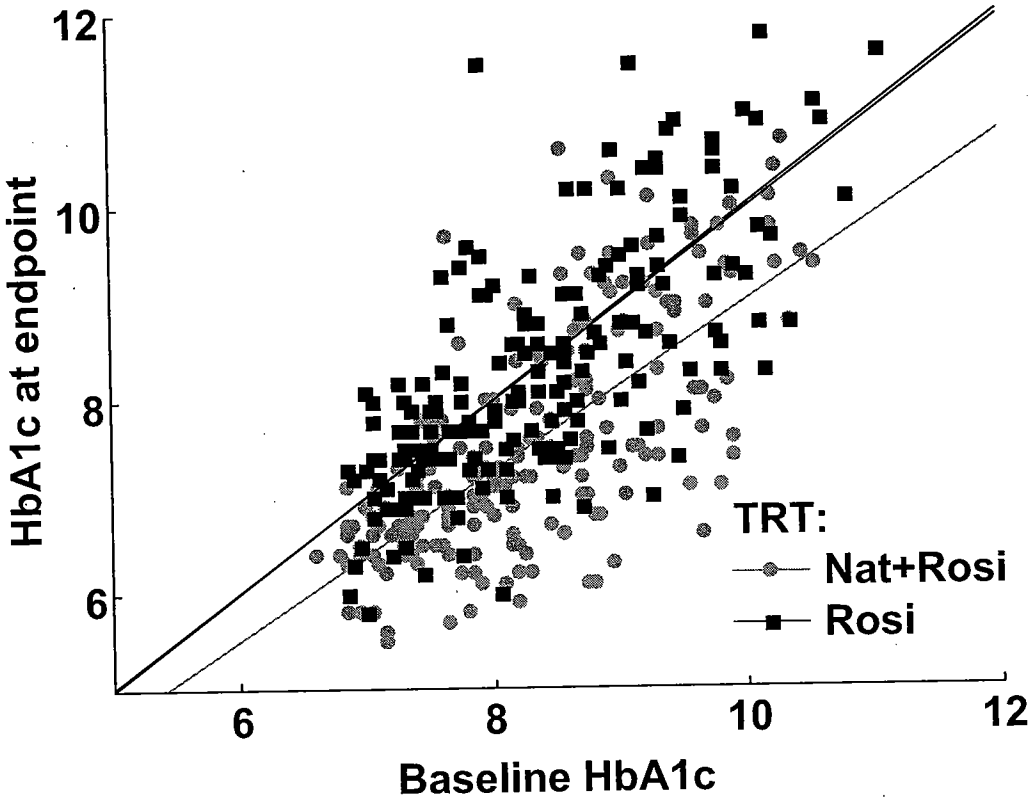
Figure 6. Boxplots of change from baseline HbA_{1c} by treatment group and median duration of diabetes



4.2.2 Baseline HbA_{1c} and Change during the Run-in Period

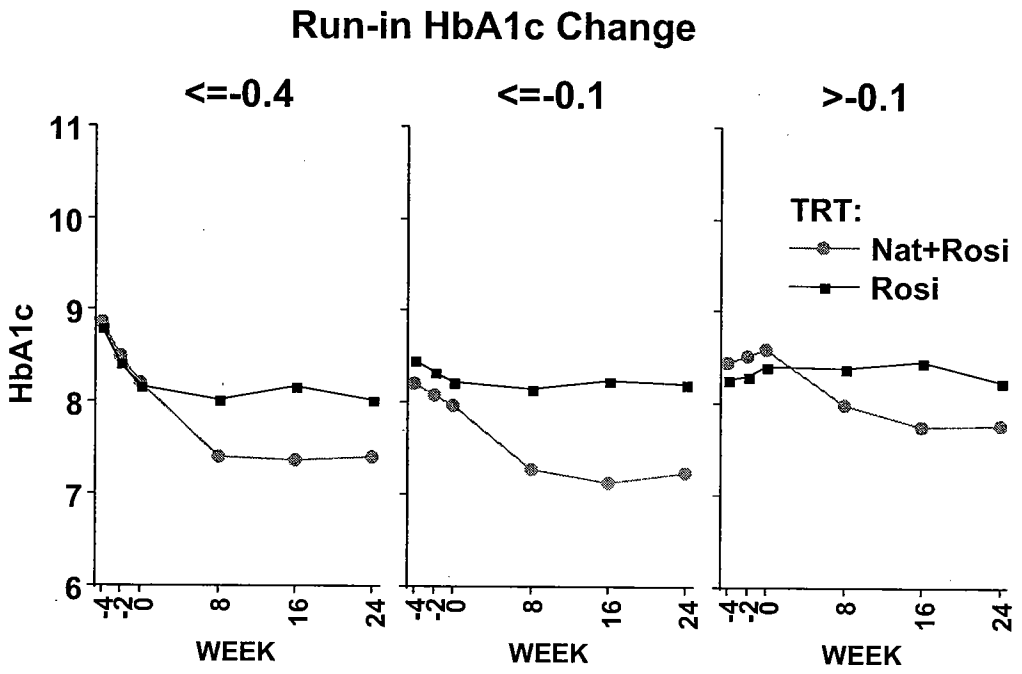
A plot of HbA_{1c} at endpoint by baseline HbA_{1c} shows that the fitted line for rosiglitazone is essentially superimposed over the identity line suggesting no change in HbA_{1c} on average within the monotherapy group. The magnitude of the treatment difference is represented by the difference between the fitted lines with slightly smaller differences seen for lower baseline values.

Figure 7. HbA_{1c} at endpoint versus baseline HbA_{1c} with a fitted line for each treatment group



It was shown earlier in this review that a change in HbA_{1c} was observed during the run-in period (see Figure 2). To examine whether the run-in change in HbA_{1c} impacted the changes observed during the randomized treatment period, this reviewer examined treatment effects by tertiles defined by run-in change. The treatment effects are about the same regardless of the change during the run-in with about a 0.7 decrease from baseline in the add-on group and essentially no change in the rosiglitazone monotherapy group.

Figure 8. HbA_{1c} at endpoint versus baseline HbA_{1c} with a fitted line for each treatment group



5. Summary and Conclusions

The single trial (Trial A2301) submitted by the sponsor demonstrated significant decreases in HbA_{1c} due to the addition of nateglinide therapy in patients considered to be inadequately controlled on rosiglitazone alone. This single trial was an add-on trial with two treatment arms (nateglinide plus rosiglitazone and rosiglitazone alone) making these trial results applicable only to patients inadequately treated with rosiglitazone. So there is no evidence provided that combination therapy in naïve patients is advantageous over monotherapy with rosiglitazone or nateglinide alone.

Statistical analyses of the data from Trial A2301 led to the following conclusions:

- The addition of nateglinide to rosiglitazone resulted in a statistically significant mean HbA_{1c} treatment effect of -0.74%
- Subgroup analyses showed consistent treatment effects regardless of age, gender, baseline HbA_{1c}, run-in change in HbA_{1c} and duration of diabetes

- Significant weight gains were seen in the combination group compared to the monotherapy group with 81% of the patients showing a weight gain at endpoint; 34% gained more than 4 kg.

6. Recommendations for labeling

Other label changes this reviewer would recommend are editorial and should be discussed with the full review team.

Joy D. Mele, M.S.
Mathematical Statistician

Concur:

Todd Sahlroot, Ph.D.
Team Leader

Ed Nevius, Ph.D.
Director of DOB2

cc:
Archival NDA
HFD-510
HFD-510/RMisbin, EColman, DOrloff
HFD-715/JMele, TSahlroot, ENevius, CAnello
Mele/x76376/DOB2/Word-rev.doc/September 11, 2003

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Joy Mele
9/22/03 11:43:28 AM
BIOMETRICS

Todd Sahlroot
9/22/03 01:00:51 PM
BIOMETRICS

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 21-204/S-006

CLINICAL PHARMACOLOGY/ BIOPHARMACEUTICS REVIEW(S)

Clinical Pharmacology and Biopharmaceutics Review
Division of Pharmaceutical Evaluation II

NDA:	21-204
Product Trade Name:	Starlix®
Active Ingredient:	Nateglinide
Dose:	60 mg or 120 mg tablet
Indication:	Oral antidiabetic agent
Sponsor:	Novartis Pharmaceuticals Corporation
Date of Submission:	December 19, 2002
Type of Submission:	Efficacy Supplement / SE1 Amendment to a pending application
Reviewer:	Leslie Kenna, Ph.D.
Team Leader:	Hae Young Ahn, Ph.D.

I. Executive Summary

This NDA was submitted in support of an expanded indication for nateglinide (Starlix®). Starlix® was approved in the United States in 2000 for use as a monotherapy or in combination with metformin to control blood glucose levels in patients with Type 2 Diabetes Mellitus. The proposed indication is for use in combination with antidiabetic drugs in the thiazolidinedione class (i.e. rosiglitazone and pioglizatone).

This application includes data from two drug interaction studies relevant to the expanded indication. Nateglinide is predominantly (~70%) metabolized by CYP2C9 with the rest (~30%) metabolized via CYP3A4. Both rosiglitazone or pioglizatone are CYP 2C8 and CYP 3A4 substrates, but probes for CYP 2C9 activity are better characterized than probes for CYP 2C8 activity. Rosiglitazone is primarily metabolized by CYP 2C8 and to a lesser extent by CYP 2C9.

Study CDJN608A2414 (Study 2414) investigated the effect of a potent and selective CYP 2C9 inhibitor (sulfinpyrazone) on the pharmacokinetics of nateglinide. Study CDJN608A2102 (Study 2102) investigated the effect of nateglinide on the pharmacokinetics and pharmacodynamics of a CYP 2C9 substrate (acenocoumarol). (Note that neither Study 2102 nor Study 2414 was directly relevant to the combination of nateglinide plus a drug in the thiazolidinedione class—the sponsor did not test rosiglitazone or pioglizatone.)

The sponsor is proposing no dosage adjustments when nateglinide and a CYP 2C9 inhibitor are coadministered. The sponsor is also proposing no dose adjustments when nateglinide and acenocoumarol are coadministered in a clinical setting.

Recommendation

NDA 21-204 is acceptable from a Clinical Pharmacology and Biopharmaceutics perspective provided that labeling comments are incorporated.

II. Table of Contents

III. Summary of Clinical Pharmacology and Biopharmaceutics Findings

In Study 2102, co-administration of 120 mg TID nateglinide and 10 mg acenocoumarol caused no change in mean tmax or mean Cmax for acenocoumarol. (Note: acenocoumarol is not marketed in the United States.) Mean $AUC_{0\rightarrow\infty}$ of S- and R-acenocoumarol increased 3.9% and 9.4%, respectively, and mean t½ of S- and R-acenocoumarol decreased 11% and 16.4%, respectively. The only statistically significant parameter change was $AUC_{0\rightarrow t}$ for R-acenocoumarol. No statistically significant difference in prothrombin time or any derived coagulation parameter was observed at any time point after acenocoumarol dosing. Nineteen (19) adverse events occurred in subjects receiving nateglinide, while eleven (11) AEs occurred in subjects receiving placebo. Nausea (in 3 subjects) and dizziness (in 3 subjects) were among the adverse events considered drug-related.

In Study 2414, co-administration of 120 mg nateglinide and 200 mg BID sulfinpyrazone caused a 27% increase in mean nateglinide exposure ($AUC_{0\rightarrow\infty}$) with a 90% confidence interval of 19-38%. There was no associated change in mean Cmax, tmax, or t½. A greater number of adverse events (AEs) occurred when nateglinide was coadministered with sulfinpyrazone (13 events in 7 subjects) compared to when nateglinide was dosed alone (5 events in 3 subjects). AEs occurring during the nateglinide/sulfinpyrazone coadministration study were generally mild in nature—loose stools (1 subject), nausea (2 subjects), fatigue (2 subjects), pain in limb (1 subject), headache (4 subjects), and rash (2 subjects).

IV. Question Based Review

1. Does Starlix® significantly impact the pharmacokinetics of acenocoumarol?

To address this question, the sponsor submitted Study 2102: "A single center, randomized, double-blind, cross-over study to investigate the effect of nateglinide (Starlix®) on the pharmacodynamics and pharmacokinetics of acenocoumarol in healthy subjects". Study 2102 was a two-period, randomized, double-blind, two-way crossover study that 12 subjects,18 to 45 years of age, completed (8 male, 4 female subjects). To evaluate the drug-drug interaction, subjects received either 120 mg nateglinide or placebo thrice daily for 5 days. On day 3 of the study, subjects received a single 10 mg acenocoumarol dose.

concentrations were determined using HPLC with UV detection techniques at a limit of quantitation of —— . Assay accuracy was 90% with a CV of 10%.

2. Does CYP 2C9 inhibition have a clinically significant impact on the pharmacokinetics of Starlix®?

To address this question, the sponsor submitted the results of Study 2414, "A randomized, open-label, two-period, crossover study to evaluate the pharmacokinetic interaction between SDZ DJN 608 (nateglinide) and sulfinpyrazone (Anturane®), a selective 2C9 inhibitor, in healthy subjects". Study 2414 is a randomized, open-label, two period, crossover study that 16 healthy males and females, aged 18 to 50 years completed. To investigate the drug interaction, subjects received 200 mg oral tablets of sulfinpyrazone twice daily for 7 days. On day 7, a single 120 mg oral dose of nateglinide was coadministered with sulfinpyrazone. A single dose of nateglinide was also dosed to each subject to establish the kinetics of nateglinide alone.

In Study 2414, coadministration with a CYP 2C9 inhibitor caused a 27% (with a 90% confidence interval of 19-38%) increase in mean nateglinide $AUC_{0\rightarrow\infty}$, with no change in mean Cmax, tmax, or t½. Note that tmax was not well estimated during either study period.

Adverse events (AE) were experienced by ~50% of subjects; all but one (moderate maculo papular rash) were considered mild in severity. A greater number of AEs occurred when nateglinide was coadministered with sulfinpyrazone (13 events in 7 subjects) compared to when nateglinide was dosed alone (5 events in 3 subjects). AEs occurring during the nateglinide/sulfinpyrazone coadministration study included loose stools (1 subject), nausea (2 subjects), fatigue (2 subjects), pain in limb (1 subject), headache (4 subjects), and rash (2 subjects). The mean serum uric acid levels declined following dosing with sulfinpyrazone (a uricosuric agent) from mean baseline of 4.31 mg/dL to 1.76 mg/dL at 72 hours postdose. This was reported as not clinically significant.

EMEA guidelines recommend using sulfinpyrazone as a potent CYP 2C9 inhibitor. The dose of sulfinpyrazone used in this study was its usual daily maintenance dose. Sulfinpyrazone was dosed 200 mg twice daily for 6 days before coadministration on day 7 with nateglinide. The half life of sulfinpyrazone is 4 hours[3], thus, subjects reached steady state levels of sulfinpyrazone by the time nateglinide was coadministered. Tmax for sulfinpyrazone occurs 1-2 hours post dose[4], thus, dosing sulfinpyrazone and nateglinide simultaneously aimed to have the Cmax for the drugs coincide for the maximum interaction potential.

An adequate number of blood samples were drawn post-nateglinide dosing on day 7 to characterize nateglinide pharmacokinetics. The assays used measure nateglinide plasma concentrations were of adequate sensitivity; nateglinide concentrations were determined using HPLC with UV detection techniques at a limit of quantitation of / (Assay accuracy was 90% with a CV of 10%.

References

[1] Henk H. Thijssen, Jean-Pierre Flinois, and Phillippe H. Beaune. Cytochrome P4502C9 Is the Principal Catalyst of Racemic Acenocoumarol Hydroxylation Reactions in Human Liver Microsomes. Drug Metabolism and Disposition Vol. 28, Issue 11, 1284-1290, November 2000.

[2] Physician's Desk Reference, December 2002.

[3] Bradbrook ID, John VA, Morrison PJ, Rogers HJ, Spector RG. Pharmacokinetics of single doses of suphinpyrazone and its major metabolites in plasma and urine. Br J Clin Pharmacol. 1982 Feb; 13(2): 177-185.

[4] Dieterle W, Faigle JW, Mory H, Richter WJ, Theobald W. Biotransformation and pharmacokinetics of sulfinpyrazone (Anturane) in man. Eur J Clin Pharmacol. 1975 Dec 19;9(2-3):135-45.

V. Detailed Labeling Recommendations

Refer to the Appendix for a marked up version of the proposed package insert. The recommended changes based on this review are indicated in red type.

- It is recommended that the sponsor move the following sections of the label from the "Drug Interactions" component of "PRECAUTIONS" to "Clinical Pharmacology" section because no significant drug-drug interactions were reported.

In vitro drug metabolism studies indicate that Starlix is predominantly metabolized by the cytochrome P450 isozyme CYP2C9 (70%) and to a lesser extent CYP3A4 (30%). Starlix is a potential inhibitor of the CYP2C9 isoenzyme *in vivo* as indicated by its ability to inhibit the *in vitro* metabolism of tolbutamide. Inhibition of CYP 3A4 metabolic reactions was not detected in *in vitro* experiments.

Glyburide: In a randomized, multiple-dose crossover study, patients with Type 2 diabetes were administered 120 mg Starlix three times a day before meals for 1 day in combination with glyburide 10 mg daily. There were no clinically relevant alterations in the pharmacokinetics of either agent.

Metformin: When Starlix 120 mg three times daily before meals was administered in combination with metformin 500 mg three times daily to patients with Type 2 diabetes, there were no clinically relevant changes in the pharmacokinetics of either agent.

Digoxin: When Starlix 120 mg before meals was administered in combination with a single 1 mg dose of digoxin to healthy volunteers, there were no clinically relevant changes in the pharmacokinetics of either agent.

Warfarin: When healthy subjects were administered Starlix 120 mg three times daily before meals for four days in combination with a single dose of warfarin 30 mg on day 2, there were no alterations in the pharmacokinetics of either agent. Prothrombin time was not affected.

Diclofenac: Administration of morning and lunch doses of Starlix 120 mg in combination with a single 75 mg dose of diclofenac in healthy volunteers resulted in no significant changes to the pharmacokinetics of either agent.

13 Page(s) Withheld

_____ § 552(b)(4) Trade Secret / Confidential

X § 552(b)(4) Draft Labeling

_____ § 552(b)(5) Deliberative Process

Withheld Track Number: Clin Pharm/Bio- 21-204
5006

Storage

Store at 25° C (77° F); excursions permitted to 15° C -30° C (59° F -86° F).

Dispense in a tight container, USP.

B. Individual Study Reviews

1. Study CDJN608A2102:

A single center, randomized, double-blind, cross-over study to investigate the effect of nateglinide (Starlix®) on the pharmacodynamics and pharmacokinetics of acenocoumarol in healthy subjects.

Design

- Two-period, randomized, double-blind, two-way crossover study
- N=14; 12 completed (8 male, 4 female subjects), 18-45 years
- Schema:

Treatment A

Day 1 120 mg TID nateglinide (Starlix®)
Day 2 120 mg TID nateglinide
Day 3 120 mg TID nateglinide + single 10 mg acenocoumarol dose*
Day 4 120 mg TID nateglinide
Day 5 120 mg TID nateglinide

Treatment B

Day 1 placebo
Day 2 placebo
Day 3 placebo + single 10 mg acenocoumarol dose*
Day 4 placebo
Day 5 placebo

*Acenocoumarol dose: 2 x [redacted] + 2 x [redacted]

- 7 day washout between treatment periods
- Starlix® and placebo dosed 10 minutes before a meal
- Blood samples drawn:

Acenocoumarol	0, .25, .5, 1, 1.5, 2, 3, 5, 8, 12, 24, 36, 48, 72 hours
Nateglinide	Trough levels for midday and evening doses
	5 hours post evening dose

Methods

Measurements

1. R-acenocoumarol and S-acenocoumarol plasma concentrations
- Performed using an LC-MS/MS assay
- Limit of quantification of [redacted] for each enantiomer

2. Anticoagulant parameters measured
- Prothrombin time (PT)
- International Normalized Ratio Prothrombin Time (PT INR)

• PT and PT INR measurement schema:
Day –1 (baseline) At screening
Day 3 0, 8, 12, 24, 36, 48, 72 hours post-acenocoumarol dose
Anticoagulant parameters were also measured at the end of the study

3. Nateglinide concentrations
• Determined using HPLC with UV detection techniques
• Limit of quantitation of [illegible]
• Assay accuracy: 90%, CV: 10%

Results
Table 1 shows the pharmacokinetic parameters for each acenocoumarol enantiomer after nateglinide coadministration versus coadministration with placebo.

	S-acenocoumarol		R-acenocoumarol	
	+ Nateglinide	**+ Placebo**	**+ Nateglinide**	**+ Placebo**
tmax (hr)	1.0 (1-3)	1.0 (0.5-1)	2.5 (1-5)	2.5 (1-5)
Cmax (ng/mL)	142.1 (36)	141.0 (34)	316.4 (16)	304.6 (16)
$AUC_{0\to t}$ (ng hr / mL)	397.0 (20)	382.4 (23)	4217 (23)	3831 (24)
$AUC_{0\to\infty}$ (ng hr / mL)	402.4 (20)	387.3 (23)	4334 (23)	3962 (24)
t½ (hr)	3.88 (58)	4.36 (43)	16.8 (30)	20.1 (23)

Table 1. Mean (CV%) pharmacokinetic parameters of S-acenocoumarol following 10 mg single oral dose of acenocoumarol administered with placebo or with 120 mg oral doses of nateglinide. Note that tmax is reported as the median (range).

Note the following on the PK parameters reported in Table 1:
• No change in mean absorption parameters tmax or Cmax for acenocoumarol, however, the range of S-acenocoumarol tmax increases upon coadministration with nateglinide
• Simple ratio of mean $AUC_{0\to\infty}$ of S- and R- acenocoumarol increases 3.9% and 9.4%, respectively
• Simple ratio of mean t½ of S- and R- acenocoumarol decreases 11% and 16.4%, respectively
• The mechanism for an increase in $AUC_{0\to\infty}$, despite a decrease in t½, was not explained. The variability in t½, however, makes the change in t½ possibly an artefact of imprecision in measurement.

Table 2 shows the statistics on AUC and Cmax for the two enantiomers of acenocoumarol.

	Parameter	Least-squares mean ratio	90% Confidence Interval
S-acenocoumarol	**$AUC_{0\to t}$**	1.05	(0.97, 1.13)
	Cmax	1.00	(0.81, 1.24)

R-acenocoumarol	$AUC_{0\rightarrow t}$	1.11	(1.06, 1.16)
	Cmax	1.04	(0.92, 1.17)

Table 2. Least-squares mean ratio and 90% confidence intervals of pharmacokinetic parameters from ANOVA of acenocoumarol coadministered with nateglinide versus coadministration with placebo. The ratio of least-squares means and the 90% confidence interval were obtained from the analysis of log-transformed data.

Note in Table 2:

• The only statistically significant parameter change is $AUC_{0\rightarrow t}$ for R-acenocoumarol (its 90% confidence interval does not include 1). On average, the least-squares mean ratio change in this parameter is an increase of 11%.

Table 3 and Table 4 show the pharmacodynamic parameters for acenocoumarol with and without nateglinide coadministration. The data from 11 subjects were included in the pharmacodynamic analysis. The data from one subject—whose plasma concentrations of acenocoumarol were very low in treatment B compared to his own in treatment A and compared to other subjects in treatment B—was not used.

	Mean (CV%)		p-value
	Acenocoumarol + Nateglinide	Acenocoumarol + Placebo	
RAW DATA			
PT tmax (median)	24 (14)	24 (26)	>0.05
PTmax	20.0 (17)	18.7 (13)	>0.05
AUC_{PT}	1170.4 (10)	1136.0 (8)	>0.05
CHANGE FROM PREDOSE			
PT tmax (median)	24 (14)	24 (26)	>0.05
PTmax	6.2 (45)	5.0 (38)	>0.05
AUC_{PT}	175.5 (44)	150.2 (35)	>0.05

Table 3. Mean pharmacodynamic parameters and statistical comparisons of prothrombin time following 10 mg single oral dose of acenocoumarol administered with placebo or with 120 mg oral doses of nateglinide.

	Mean (CV%)		p-value
	Acenocoumarol + Nateglinide	Acenocoumarol + Placebo	
RAW DATA			
PT INRtmax (median)	24 (14)	24 (26)	>0.05
PT INRmax	1.88 (21)	1.72 (16)	>0.05
$AUC_{PT\ INR}$	103.5 (13)	99.38 (10)	>0.05
CHANGE FROM PREDOSE			
PT INRtmax (median)	24 (14)	24 (26)	>0.05
PT INRmax	0.72 (47)	0.57 (40)	>0.05
$AUC_{PT\ INR}$	20.14 (46)	16.67 (37)	>0.05

Table 4. Mean derived pharmacodynamic parameters and statistical comparisons of PT INR following 10 mg single oral dose of acenocoumarol administered with placebo or with 120 mg oral doses of nateglinide.

Note in Table 3 and Table 4:
• No statistically significant difference in prothrombin time at any time point or any derived parameter after acenocoumarol dosing

Safety and Tolerability
• If a subject reported an adverse event more than one time during each study period, it was counted only as one adverse event.
• 8 of the 14 subjects experienced a total of 30 adverse events (AEs).
• 19 AEs occurred in subjects receiving nateglinide, while 11 AEs occurred in subjects receiving placebo.
• Back pain (1 versus 0 event), dizziness (3 versus 0 events), nausea (3 versus 1 event), and chest pain (1 versus 0 event) were among the events occuring more frequently in subjects receiving nateglinide than in subjects receiving placebo.
• Nausea was considered drug related in all 3 subjects; it was of mild intensity in 2 subjects and of moderate intensity in 1 subject.
• Dizziness was considered drug related in all 3 subjects; it was of mild intensity in 1 subject and of moderate intensity in 2 subjects.

2. Study CDJN608A2414
A randomized, open-label, two-period, crossover study to evaluate the pharmacokinetic interaction between SDZ DJN 608 (nateglinide) and sulfinpyrazone [redacted], a selective 2C9 inhibitor, in healthy subjects

Design
• Randomized, open-label, two period, crossover
• N=18 healthy males and females, 18-50 years enrolled; 16 completed
• 2 Treatment sequences

Treatment A
Single 120 mg oral dose nateglinide

Treatment B

Days 1-6	200 mg b.i.d. oral dose sylfinpyrazone tablets
Day 7	200 mg b.i.d. oral dose sylfinpyrazone tablets + single 120 mg oral dose nateglinide

• 2-week period washout between Treatment A and Treatment B
• Blood were samples drawn: 0, .5, 1, 1.5, 2, 3, 4, 6, 8, 12, 16, 24 hours post-dose
• EMEA guidelines recommend using sulfinpyrazone as a potent CYP 2C9 inhibitor; dose is its usual daily maintenance dose

Methods
Nateglinide concentration measurement:
• Determined using HPLC with UV detection techniques
• Limit of quantitation of [redacted]
• Assay accuracy: 90%, CV: 10%

Results

Table 1 shows the pharmacokinetic parameters observed.

Treatment	Cmax (ng/mL)	$AUC_{0\rightarrow t}$	$AUC_{0\rightarrow\infty}$	tmax (hr)	t½ (hr)	kel (/hr)
Nateglinide	8471 +/- 3525	18058 +/- 4324	18364 +/- 4273	0.8 +/- 0.9	1.8 +/- 0.3	0.4 +/- 0.07
Nateglinide + Sulfinpyrazone	8246 +/- 3150	22947 +/- 4287	23251 +/- 4287	0.9 +/- 0.8	2.0 +/- 0.3	0.36 +/- 0.04
Ratio: Nateglinide + sulfinpyrazone / nateglinide alone	0.97	1.27	1.27			
90% CI	0.86-1.13	1.19-1.38	1.19-1.37			

Table 1. Mean (+/- SD) Pharmacokinetic and statistical parameters of nateglinide when administered alone or in combination with sulfinpyrazone. 90% CI for the true ratio determined from an ANOVA model for the natural log-transformed data.

Note in Table 1:

- 27% (with a 90% confidence interval of 19-38%) increase in mean $AUC_{0\rightarrow\infty}$
- No change in mean Cmax, tmax, or t½
- tmax was not well estimated for either regimen

Safety and Tolerability

- Adverse events (AE) were experienced by ~50% of subjects; all but one (moderate maculo papular rash) were considered mild in severity.
- A greater number of AEs occurred when nateglinide was coadministered with sulfinpyrazone (13 events in 7 subjects) compared to when nateglinide was dosed alone (5 events in 3 subjects).
- AEs occurring during the nateglinide/sulfinpyrazone coadministration study included: loose stools (1 subject), nausea (2 subjects), fatigue (2 subjects), pain in limb (1 subject), headache (4 subjects), and rash (2 subjects).
- The moderate AE—maculo papular rash—occurred in one subject following nateglinide only treatment; study drug was discontinued in this subject.
- The mean serum uric acid levels declined following dosing with sulfinpyrazone (a uricosuric agent) from mean baseline of 4.31 mg/dL to 1.76 mg/dL at 72 hours postdose. This was reported as not clinically significant.

C. Consult Review

None requested

D. Cover Sheet and OCPB Filing/Review Form

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Leslie Kenna
9/16/03 05:32:45 PM
BIOPHARMACEUTICS

Hae-Young Ahn
9/17/03 04:05:35 PM
BIOPHARMACEUTICS

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 21-204/S-006

ADMINISTRATIVE DOCUMENTS AND CORRESPONDENCE

EXCLUSIVITY SUMMARY for NDA # 21-204 SUPPL #006

Trade Name: Starlix Tablets Generic Name: Nateglinide

Applicant Name: Novartis HFD-510

Approval Date: October 20, 2003

PART I: IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, but only for certain supplements. Complete Parts II and III of this Exclusivity Summary only if you answer "YES" to one or more of the following questions about the submission.

   a) Is it an original NDA? YES/_/ NO /_✔__/

   b) Is it an effectiveness supplement? YES /_✔__/ NO /__/

      If yes, what type(SE1, SE2, etc.)? SE-1

   c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "NO.")

      YES /_✔/ NO /___/

      If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

      If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

   d) Did the applicant request exclusivity?

      YES /___/ NO /_✔/

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

e) Has pediatric exclusivity been granted for this Active Moiety?

YES /___/ NO /✔/

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.

2. Has a product with the same active ingredient(s), dosage form, strength, route of administration, and dosing schedule previously been approved by FDA for the same use? (Rx to OTC) Switches should be answered No - Please indicate as such).

YES /_/ NO /✔/

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.

3. Is this drug product or indication a DESI upgrade?

YES /___/ NO /✔/

IF THE ANSWER TO QUESTION 3 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9 (even if a study was required for the upgrade).

PART II: FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES
(Answer either #1 or #2, as appropriate)

1. Single active ingredient product:
Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved.

Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES /✔/ NO /_/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA 21-204 Starlix (nateglinide tablets).

2. Combination product.

If the product contains more than one active moiety (as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES /__/ NO /✔/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9. IF "YES," GO TO PART III.

PART III: THREE-YEAR EXCLUSIVITY FOR NDA'S AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2, was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a).

If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES /✔/ NO /__/

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

For the purposes of this section, studies comparing two products with the same ingredient(s) are considered to be bioavailability studies.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES /✔/ NO /___/

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval **AND GO DIRECTLY TO SIGNATURE BLOCK ON Page 9:**

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES /___/ NO /✔/

(1)If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES /___/ NO /___/

If yes, explain:

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES /___/ NO /✔/

If yes, explain:

(c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Investigation #1, Study # 2301

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

(a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1 YES /___/ NO /✔/

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

NDA # _____ Study #
NDA # _____ Study #
NDA # _____ Study #

(b) For each investigation identified as "essential to the approval," does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1 YES /___/ NO /___/

Investigation #2 YES /___/ NO /___/

Investigation #3 YES /___/ NO /___/

If you have answered "yes" for one or more investigations, identify the NDA in which a similar investigation was relied on:

NDA # _____ Study #

NDA # _____ Study #

NDA # _____ Study #

(c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

Investigation #__, Study # 2301

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

(a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1

IND 47,235 YES /✔/ ! NO /___/ Explain:

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1

YES /___/ Explain _____ ! NO /___/ Explain _____

_____ ! _____

_____ ! _____

Investigation #2

YES /___/ Explain _____ ! NO /___/ Explain _____

_____ ! _____

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES /___/ NO /✔/

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Jena Weber
11/14/03 12:57:21 PM

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

PROJECT MANAGER LABELING REVIEW

Application Number: 21-204/S-006

Name of Drug: Starlix® (nateglinide) Tablets, 60 mg and 120 mg

Sponsor: Novartis Pharmaceuticals

Material Reviewed: Final agreed-upon text for the package insert labeling (FPL).

Submission Dates: December 19, 2002, amended October 20, 2003 (via fax).

Receipt Dates: December 20, 2002, and October 20, 2003 (via fax).

Background and Summary: The NDA for Starlix tablets was approved on December 22, 2000, and is indicated as monotherpy as an adjunct to diet and exercise to improve glycemic control in patients with type 2 diabetes mellitus. In addition, Starlix may be used concomitantly with metformin to improve glycemic control.

Review: This supplemental new drug application provides for an expanded indication for use in combination with antidiabetic drugs in the thiazolidinedione class. No changes were made to the carton or container labels. The following PI changes are as follows:

Under the **CLINICAL PHARMACOLOGY** section, **Starlix Combination Therapy** subsection, **Rosiglitazone** subsection:

- **A 24-week, double-blind multicenter, placebo-controlled trial was performed in patients with type 2 diabetes not adequately controlled on rosiglitazone monotherapy 8 mg daily. addition of Starlix (120 mg three times per day with meals) was associated with statistically signficantly greater reductions in HbA1c compared to rosiglitazone monotherapy. The difference was –0.77% at 24 weeks. The mean change in weight from baseline was about 3 kg for patients treated with Starlix plus rosiglitazone vs about 1 kg for patients treated with placebo plus rosiglitazone.**

Under the **INDICATIONS AND USAGE** section:

- Paragraph 3 should state:

The following 6 paragraphs were moved from the **PRECAUTIONS** section, **Drug Interactions** subsection, to the **CLINICAL PHARMACOLGY** section, **Pharmacokinetics** subsection, **Drug Interactions** subsection:

Drug Interactions

In vitro drug metabolism studies indicate that Starlix is predominantly metabolized by the cytochrome P450 isozyme CYP2C9 (70%) and to a lesser extent CYP3A4 (30%). Starlix is a potential inhibitor of the CYP2C9 isoenzyme *in vivo* as indicated by its ability to inhibit the *in vitro* metabolism of tolbutamide. Inhibition of CYP 3A4 metabolic reactions was not detected in *in vitro* experiments.

Glyburide: In a randomized, multiple-dose crossover study, patients with Type 2 diabetes were administered 120 mg Starlix three times a day before meals for 1 day in combination with glyburide 10 mg daily. There were no clinically relevant alterations in the pharmacokinetics of either agent.

Metformin: When Starlix 120 mg three times daily before meals was administered in combination with metformin 500 mg three times daily to patients with Type 2 diabetes, there were no clinically relevant changes in the pharmacokinetics of either agent.

Digoxin: When Starlix 120 mg before meals was administered in combination with a single 1 mg dose of digoxin to healthy volunteers, there were no clinically relevant changes in the pharmacokinetics of either agent.

Warfarin: When healthy subjects were administered Starlix 120 mg three times daily before meals for four days in combination with a single dose of warfarin 30 mg on day 2, there were no alterations in the pharmacokinetics of either agent. Prothrombin time was not affected.

Diclofenac: Administration of morning and lunch doses of Starlix 120 mg in combination with a single 75 mg dose of diclofenac in healthy volunteers resulted in no significant changes to the parmacokinetics of either agent.

Conclusion: The draft PI label submitted for supplement 006 (no identifier code noted) was compared to latest approved package insert, (December 22, 2000 – no identifier code). Changes are acceptable; no other modifications have been identified. Issue approval (AP) letter.

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/s/

Jena Weber
10/27/03 12:12:49 PM
CSO

Jena Weber
10/27/03 12:14:54 PM
CSO

Division of Metabolic and Endocrine Drug Products

ADMINISTRATIVE REVIEW OF NEW DRUG APPLICATION

Application Number: 21-204

Name of Drug: Starlix (nateglinide) Tablets, 60 mg & 120 mg

Sponsor: Novartis

Material Reviewed

Type of Submission (i.e., paper, electronic, or combination): Combination

Submission Date: December 19, 2002.

Receipt Date: December 20, 2002.

Filing Date: February 12, 2003.

User-fee Goal Date: October 20, 2003.

Proposed Indication: For use in combination with antidiabetic drugs in the thiazolidinedione class.

Review

PART I: OVERALL FORMATTING[a,d,e]

[Note: Items 1,2,3,4, & 5 must be submitted in paper.]	Y	N	COMMENTS (If paper: list volume & page numbers) (If electronic: list folder & page numbers)
1. Cover Letter	✔		Vol. 1.1
2. Form FDA 356h (original signature)	✔		Vol. 1.1
a. Establishment information (facilities ready for inspection?)		✔	~~NN~~ ~~NN~~
b. Reference to DMF(s) & Other Applications			

3. User Fee FDA Form 3397 4. Patent information & certification	✔		Vol. 1.1
5. Debarment certification (Note: Must have a definitive statement)	✔		Vol. 1.1
6. Field Copy Certification			NN
7. Financial Disclosure	✔		Vol. 1.1
8. Comprehensive Index	✔		Vol. 1.1
9. Pagination	✔		Vol. 1.1
10. Summary Volume	✔		Vol. 1.1
11. Review Volumes	✔		
12. Labeling (PI, container, & carton labels)	✔		Vol. 1.1
a. unannotated PI	✔		
b. annotated PI	✔		Vol. 1.1
c. immediate container			N/A
d. carton			N/A
e. patient package insert (PPI)			N/A
f. foreign labeling (English translation)		✔	N/A
13. Case Report Tabulations (CRT) (paper or electronic) (by individual patient data listing or demographic)	✔		Electronic
14. Case Report Forms (paper or electronic) (for death & dropouts due to adverse events)	✔		Electronic

Y=Yes (Present), N=No (Absent)

PART II: SUMMARY[b,d,e]

	Y	N	COMMENTS (If paper: list volume & page numbers) (If electronic: list folder & page numbers)
1. Pharmacologic Class, Scientific Rationale, Intended Use, & Potential Clinical Benefits		✔	N/A
2. Foreign Marketing History	✔		Vol. 1.1
3. Summary of Each Technical Section	✔		Vol. 1.1
a. Chemistry, Manufacturing, & Controls (CMC)		✔	N/A
b. Nonclinical Pharmacology/Toxicology		✔	N/A
c. Human Pharmacokinetic & Bioavailability	✔		Vol. 1.1
d. Microbiology			N/A
e. Clinical Data & Results of Statistical Analysis			N/A
4. Discussion of Benefit/Risk Relationship & Proposed Postmarketing Studies	✔		Vol. 1.1
5. Summary of Safety	✔		Vol. 23
6. Summary of Efficacy	✔		Vol. 23

Y=Yes (Present), N=No (Absent)

PART III: CLINICAL/STATISTICAL SECTIONS[c,d,e]

	Y	N	COMMENTS (If paper: list volume & page numbers) (If electronic: list folder & page numbers)
1. List of Investigators	✔		1.1

2. Controlled Clinical Studies	✔		Vol.
a. Table of all studies			
b. Synopsis, protocol, related publications, list of investigators, & integrated clinical & statistical report for each study (including completed, ongoing, & incomplete studies)	✔		
c. Optional overall summary & evaluation of data from controlled clinical studies	✔		
3. Integrated Summary of Efficacy (ISE)	✔		Vol. 23
4. Integrated Summary of Safety (ISS)	✔		Vol. 23
5. Drug Abuse & Overdosage Information		✔	N/A
6. Integrated Summary of Benefits & Risks of the Drug	✔		Vol. 23
7. Gender/Race/Age Safety & Efficacy Analysis of Studies			

Y=Yes (Present), N=No (Absent)

PART IV: MISCELLANEOUS[d,e]

	Y	N	COMMENTS (list volume & page numbers) (If electronic: list folder & page numbers)
1. Written Documentation Regarding Drug Use in the Pediatric Population			
2. Review Aids (Note: In electronic submission, can only request aids if increase functionality. In paper submission, verify that aids contain the exact information duplicated on paper. Otherwise, the aids are considered electronic submissions.)		✔	N/A
a. Proposed unannotated labeling in	✔		

MS WORD			1.1
b. Stability data in SAS data set format (only if paper submission)		✔	N/A
c. Efficacy data in SAS data set format (only if paper submission)		✔	
d. Biopharmacological information & study summaries in MS WORD (only if paper submission)	✔		
e. Animal tumorigenicity study data in SAS data set format (only if paper submission)			N/A
3. Exclusivity Statement (optional)			N/A

Y=Yes (Present), N=No (Absent)

Conclusions: AP

Jena Weber
Regulatory Project Manager

ADMINISTRATIVE REVIEW

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/s/

Jena Weber
10/20/03 02:37:48 PM
CSO

Jena Weber
10/20/03 02:39:48 PM
CSO

NDA REGULATORY FILING REVIEW
(Including Memo of Filing Meeting)

NDA 21-204 Supplement/-006 SE1

Trade Name: Starlix
Generic Name: Nateglinide Tablets
Strengths: 60 mg and 120 mg

Applicant: Novartis

Date of Application: December 19, 2002
Date of Receipt: December 20, 2002
Date clock started after UN: N/A
Date of Filing Meeting: February 12, 2003
Filing Date: February 18, 2003
User Fee Goal Date: October 20, 2003

Indication requested: For use in combination with antidiabetic drugs in the thiazolidinedione class.

Type of Application: Original (b)(1) NDA __✔___ Original (b)(2) NDA _____
(b)(1) Supplement _____ (b)(2) Supplement _____
[If the Original NDA was a (b)(2), all supplements are (b)(2)s; if the Original NDA was a (b)(1), the supplement can be either a (b)(1) or a (b)(2).]

NOTE: If the application is a 505(b)(2) application, complete the 505(b)(2) section at the end of this summary.

Therapeutic Classification: S
Resubmission after a withdrawal? No Resubmission after a refuse to file? No
Chemical Classification: (1,2,3 etc.) 1
Other (orphan, OTC, etc.) N/A

User Fee Status: Paid ___✔ Waived (e.g., small business, public health) _____
Exempt (orphan, government) _____
Form 3397 (User Fee Cover Sheet) submitted: YES
User Fee ID / ——— /
Clinical data? YES

Is there any 5-year or 3-year exclusivity on this active moiety in either a (b)(1) or a (b)(2) application?

NO

If yes, explain:

Does another drug have orphan drug exclusivity for the same indication? NO

If yes, is the drug considered to be the same drug according to the orphan drug definition of sameness [21 CFR 316.3(b)(13)]?

NO

Is the application affected by the Application Integrity Policy (AIP)? NO
If yes, explain.

If yes, has OC/DMPQ been notified of the submission? N/A

- Does the submission contain an accurate comprehensive index? YES
- Was form 356h included with an authorized signature? YES
  If foreign applicant, both the applicant and the U.S. agent must sign.
- Submission complete as required under 21 CFR 314.50? YES
  If no, explain:
- If an electronic NDA, does it follow the Guidance? YES
  If an electronic NDA, all certifications must be in paper and require a signature.
  Which parts of the application were submitted in electronic format?

  Additional comments:
- If in Common Technical Document format, does it follow the guidance? N/A
- Is it an electronic CTD? N/A
  If an electronic CTD, all certifications must be in paper and require a signature.
  Which parts of the application were submitted in electronic format?

  Additional comments:
- Patent information included with authorized signature? YES
- Exclusivity requested? NO
  Note: An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.
- Correctly worded Debarment Certification included with authorized signature? YES
  If foreign applicant, both the applicant and the U.S. Agent must sign the certification.

  NOTE: Debarment Certification must have correct wording, e.g.: "I, the undersigned, hereby certify that _____ Co. did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug and Cosmetic Act in connection with the studies listed in Appendix ____." Applicant may not use wording such as "To the best of my knowledge . . . ."
- Financial Disclosure information included with authorized signature? YES
  (Forms 3454 and/or 3455 must be used and must be signed by the APPLICANT.)
- Field Copy Certification (that it is a true copy of the CMC technical section)? NO

Refer to 21 CFR 314.101(d) for Filing Requirements

- PDUFA and Action Goal dates correct in COMIS? YES
  If not, have the document room staff correct them immediately. These are the dates EES uses for calculating inspection dates.

- Drug name/Applicant name correct in COMIS? If not, have the Document Room make the corrections.

- List referenced IND numbers: IND 47,235

- End-of-Phase 2 Meeting(s)? NO
  If yes, distribute minutes before filing meeting.

- Pre-NDA Meeting(s)? NO
  If yes, distribute minutes before filing meeting.

Project Management

- Package insert consulted to DDMAC? NO

- Trade name (plus PI and all labels and labeling) consulted to ODS/Div. of Medication Errors and Technical Support? NO

- MedGuide and/or PPI (plus PI) consulted to ODS/Div. of Surveillance, Research and Communication Support?
  NO

- If a drug with abuse potential, was an Abuse Liability Assessment, including a proposal for scheduling, submitted?
  N/A

If Rx-to-OTC Switch application:

- OTC label comprehension studies, all OTC labeling, and current approved PI consulted to ODS/ Div. of Surveillance, Research and Communication Support?
  N/A

- Has DOTCDP been notified of the OTC switch application? N/A

Clinical

- If a controlled substance, has a consult been sent to the Controlled Substance Staff?
  N/A

Chemistry

- Did applicant request categorical exclusion for environmental assessment? YES
  If no, did applicant submit a complete environmental assessment?
  If EA submitted, consulted to Nancy Sager (HFD-357)?

- Establishment Evaluation Request (EER) submitted to DMPQ? NO

- If parenteral product, consulted to Microbiology Team (HFD-805)? N/A

If 505(b)(2) application, complete the following section: N/A

- Name of listed drug(s) and NDA/ANDA #:

- Describe the change from the listed drug(s) provided for in this (b)(2) application (for example, "This application provides for a new indication, otitis media" or "This application provides for a change in dosage form, from capsules to solution").

- Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA? (Normally, FDA will refuse-to-file such NDAs.)

  YES NO

- Is the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action less than that of the reference listed drug (RLD)? (See 314.54(b)(1)). If yes, the application should be refused for filing under 314.101(d)(9).

  YES NO

- Is the rate at which the product's active ingredient(s) is absorbed or otherwise made available to the site of action unintentionally less than that of the RLD? (See 314.54(b)(2)). If yes, the application should be refused for filing under 314.101(d)(9).

  YES NO

- Which of the following patent certifications does the application contain? Note that a patent certification must contain an authorized signature.

  ____ 21 CFR 314.50(i)(1)(i)(A)(1): The patent information has not been submitted to FDA.

  ____ 21 CFR 314.50(i)(1)(i)(A)(2): The patent has expired.

  ____ 21 CFR 314.50(i)(1)(i)(A)(3): The date on which the patent will expire.

  ____ 21 CFR 314.50(i)(1)(i)(A)(4): The patent is invalid, unenforceable, or will not be infringed by the manufacture, use, or sale of the drug product for which the application is submitted.

  IF FILED, and if the applicant made a "Paragraph IV" certification [21 CFR 314.50(i)(1)(i)(A)(4)], the applicant must submit a signed certification that the patent holder was notified the NDA was filed [21 CFR 314.52(b)]. Subsequently, the applicant must submit documentation that the patent holder(s) received the notification ([21 CFR 314.52(e)].

____ 21 CFR 314.50(i)(1)(ii): No relevant patents.

____ 21 CFR 314.50(i)(1)(iii): The patent on the listed drug is a method of use patent and the labeling for the drug product for which the applicant is seeking approval does not include any indications that are covered by the use patent. Applicant must provide a statement that the method of use patent does not claim any of the proposed indications.

____ 21 CFR 314.50(i)(3): Statement that applicant has a licensing agreement with the patent owner (must also submit certification under 21 CFR 314.50(i)(1)(i)(A)(4) above.)
____ Written statement from patent owner that it consents to an immediate effective date upon approval of the application.

- Did the applicant:

  - Identify which parts of the application rely on information the applicant does not own or to which the applicant does not have a right of reference?

    YES NO

  - Submit a statement as to whether the listed drug(s) identified has received a period of marketing exclusivity?

    YES NO

  - Submit a bioavailability/bioequivalence (BA/BE) study comparing the proposed product to the listed drug?

    N/A YES NO

  - Certify that it is seeking approval only for a new indication and not for the indications approved for the listed drug if the listed drug has patent protection for the approved indications and the applicant is requesting only the new indication (21 CFR 314.54(a)(1)(iv).?

    N/A YES NO

- If the (b)(2) applicant is requesting exclusivity, did the applicant submit the following information required by 21 CFR 314.50(j)(4):

  - Certification that each of the investigations included meets the definition of "new clinical investigation" as set forth at 314.108(a).

    YES NO

  - A list of all published studies or publicly available reports that are relevant to the conditions for which the applicant is seeking approval.

    YES NO

  - EITHER
    The number of the applicant's IND under which the studies essential to approval were conducted.

    YES, IND # _____ NO

    OR
    A certification that it provided substantial support of the clinical investigation(s) essential to approval if it was not the sponsor of the IND under which those clinical studies were conducted?

    N/A YES NO

- Has the Director, Div. of Regulatory Policy II, HFD-007, been notified of the existence of the (b)(2) application?

YES NO

ATTACHMENT

MEMO OF FILING MEETING

DATE: Wed. February 12, 2003

BACKGROUND: Original NDA approved December 22, 2000, for use in patients with type 2 diabetes mellitus.

ATTENDEES: Robert Misbin, M.D. Steven Johnson, PharmD. Hae-Young Ahn, Ph.D.
Todd Sahlroot, Ph.D. Xavier Ysern, Ph.D. Jena Weber, BS

ASSIGNED REVIEWERS: As above, except Dr. Kenna for Dr. Johnson.

Discipline	**Reviewer**
Medical:	Robert Misbin, M.D.
Secondary Medical:	
Statistical:	Joy Mele, MS
Pharmacology:	NN
Statistical Pharmacology:	NN
Chemist:	Xavier Ysern, Ph.D.
Environmental Assessment (if needed):	NN
Biopharmaceutical:	Leslie Kenna, Ph.D.
Microbiology, sterility:	NN
Microbiology, clinical (for antimicrobial products only):	NN
DSI:	NN
Regulatory Project Manager:	Jena Weber, BS
Other Consults:	NN

Per reviewers, are all parts in English or English translation? YES
If no, explain:

CLINICAL FILE

- Clinical site inspection needed: NO
- Advisory Committee Meeting needed? NO
- If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance? N/A

CLINICAL MICROBIOLOGY	N/A
STATISTICS	FILE
BIOPHARMACEUTICS	FILE
• Biopharm. inspection needed:	NO
PHARMACOLOGY	NN
• GLP inspection needed:	NO
CHEMISTRY	FILE
• Establishment(s) ready for inspection?	NO
• Microbiology	NO
ELECTRONIC SUBMISSION: Any comments:	NO

REGULATORY CONCLUSIONS/DEFICIENCIES:

The application, on its face, appears to be well organized and indexed. The application appears to be suitable for filing.

No filing issues have been identified.

ACTION ITEMS:

Document filing issues/no filing issues conveyed to applicant by Day 74.

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/s/

Jena Weber
10/20/03 02:48:00 PM
CSO

Jena Weber
10/20/03 02:50:36 PM
CSO

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation ODE II

FACSIMILE TRANSMITTAL SHEET

DATE: October 17, 2003

To: Carl Schlotfeldt Drug Regulatory Affairs	**From:** Jena Weber Project Manager
Company: Novartis Pharmaceuticals Corp.	Division of Metabolic and Endocrine Drug Products, HFD-510
Fax number: (973) 781-3590	**Fax number:** 301-443-9282
Phone number: (862) 778-3570	**Phone number:** 301-827-6422

Subject: Reference NDA 21-204/S-006; FDA recommended labeling changes to Starlix package insert.

Total no. of pages including cover: 1

Comments: See attached page.

Document to be mailed: ☐ YES ☑ NO

Table 3 and accompanying text should be replaced by:

> A 24-week, double-blind multicenter, placebo-controlled trial was performed in patients with type 2 diabetes not adequately controlled on rosiglitazone monotherapy 8 mg daily. [redacted] addition of Starlix (120 mg three times per day with meals) was associated with statistically significantly greater reductions in HbA1c compared to rosiglitazone monotherapy. The difference was –0.77% at 24 weeks. The mean change in weight from baseline was about +3 kg for patients treated with Starlix plus rosiglitazone vs about +1 kg for patients treated with placebo plus rosiglitazone.

Under **INDICATIONS AND USAGE** section:

[redacted]

Paragraph 3 should state:

[redacted]

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/s/

Mary Parks
10/17/03 02:58:35 PM
for Dr. Orloff

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation ODE II

FACSIMILE TRANSMITTAL SHEET

DATE: July 15, 2003

To: Carl Schlotfeldt Drug Regulatory Affairs	**From:** Jena Weber Project Manager
Company: Novartis Pharmaceuticals Corp.	Division of Metabolic and Endocrine Drug Products, HFD-510
Fax number: 973-781-3590	**Fax number:** 301-443-9282
Phone number: 973-781-3570	**Phone number:** 301-827-6422

Subject: Reference NDA 21-204/S-006, submitted on December 19, 2002.

Total no. of pages including cover: 2

Comments: See attached page; please submit this information in writing to your NDA file.

Document to be mailed: ☐ YES ☑ NO

1. **Subset Analysis based on previous antidiabetic therapy**

Please provide information on antidiabetic therapy before the 12 week rosiglitazone run-in.

Please perform a subset analysis for change in HbA1c based on previous therapy.

In order to simplify the analysis, the subsets may be defined as follows:

A No pharmacological treatment
B Monotherapy with a TZD
C Monotherapy with a sulfonylurea, nateglinide or repaglinide
D Monotherapy with metformin or beta glucosidase inhibitor
E Oral agents given in combination
F Any regimen including insulin

2. **Concomitant medications**

Table – 8.2-3 indicates that the following drugs were used during the randomized period:

	Number of Patients	
	Nat + RSG	RSG
Metformin –	3	1
Metformin+sulfonylurea		1
Phentermine	1	
Insulin	2	3
Orlistat	2	
Glimepiride		2

These drugs should not have been used during the randomized portion of the study, because they can affect glycemic control. Please indicate whether these patients were included in the ITT analysis. If so, please resubmit the change in HbA1c excluding these patients.

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/s/

Jena Weber
7/15/03 08:12:13 AM
CSO

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation ODE II

FACSIMILE TRANSMITTAL SHEET

DATE: April 29, 2003

To: Carl Schlotfeldt Drug Regulatory Affairs	**From:** Jena Weber Project Manager
Company: Novartis Pharmaceuticals Corp.	Division of Metabolic and Endocrine Drug Products, HFD-510
Fax number: 973-781-3590	**Fax number:** 301-443-9282
Phone number: 973-781-3570	**Phone number:** 301-827-6422

Subject: Reference NDA 21-204/S-006, submitted on December 19, 2002.

Total no. of pages including cover: 1

Comments: Please provide copies of the different consent forms that were used in your studies (clinical and pharmacokinetic/bioavailability – drug interaction studies).

Document to be mailed: ☐ YES ☑ NO

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/s/

Jena Weber
4/29/03 07:50:15 AM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

ADDENDUM - NO FILING ISSUES IDENTIFIED

NDA 21-204/S-006

Novartis Pharmaceuticals Corporation
Attention: Carl Schlotfeldt
Associate Director, Drug Regulatory Affairs
One Health Plaza
East Hanover, NJ 07936-1080

Dear Mr. Schlotfeldt:

Please refer to your December 19, 2002, supplemental new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Starlix® (nateglinide) Tablets.

We also refer to our February 13, 2003, letter specifying that this application will be filed on February 18, 2003, and requesting additional information. Also, please address the following:

> For two medications to be used together there should be evidence that each compound contributes to the efficacy of the combination. Study 2301 was a two-arm trial that compared nateglinide to placebo in patients who had not responded adequately to rosiglitazone. Nateglinide + rosiglitazone was better than rosiglitazone alone. But it is not clear from this study what rosiglitazone contributed to the efficacy of the nateglinide + rosiglitazone combination. It would be helpful to submit efficacy data that may have been obtained during the rosiglitazone-only pretreatment.

Please follow the guidance for the submission of electronic data when creating this dataset. This guidance may be found at www.fda.gov/cder/guidance. Choose Electronic Submissions and then choose #3. In the guidance document, go to K. Item 11: Case Report Tabulations (CRT's).

Our filing review is only a preliminary evaluation of the application and is not indicative of deficiencies that may be identified during our review.

If you have any questions, please call me at 301-827-6422.

Sincerely,

{See appended electronic signature page}

Jena Weber
Regulatory Health Project Manager
Division of Metabolic & Endocrine Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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/s/

Jena Weber
2/14/03 11:09:53 AM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NO FILING ISSUES IDENTIFIED

NDA 21-204/S-006

Novartis Pharmaceuticals Corporation
Attention: Carl Schlotfeldt
Associate Director, Drug Regulatory Affairs
One Health Plaza
East Hanover, NJ 07936-1080

Dear Mr. Schlotfeldt:

Please refer to your December 19, 2002, supplemental new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Starlix® (nateglinide) Tablets.

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, this application will be filed under section 505(b) of the Act on February 18, 2003, in accordance with 21 CFR 314.101(a). However, we request that you submit a new dataset for Study 2301 to our Electronic Document Room. This dataset should contain the following variables:

1. unique patient ID
2. center number
3. race
4. age
5. gender
6. treatment group
7. week (i.e. visit decoded) where zero denotes the time of randomization. Include all weeks from -4 to the last week on treatment
8. last week completed for the patient
9. completer? (1=yes patient completed whole study, 0=patient discontinued early)
10. LOCF indicator variable (1=record contains the last efficacy value on study; 0=not the last value)
11. BMI at baseline
12. Number of months previously treated with rosiglitazone
13. Hypoglycemia on study (1=yes, 0=no)

14. Please include baseline (the calculated one), value and change from baseline for the following parameters:
    HbA1c
    FPG

    Triglyceride
    Total cholesterol
    HDL
    LDL
    Hemoglobin
    Weight

Note that each record on the dataset should be uniquely identifiable by the patient ID, and week. The data for each week should be the observed data with the LOCF data flagged by an indicator variable. All variables should be **numeric** variables and **unformatted**.

Also, please provide a summary of the run-in clinical data.

Please follow the guidance for the submission of electronic data when creating this dataset. This guidance may be found at www.fda.gov/cder/guidance. Choose Electronic Submissions and then choose #3. In the guidance document, go to K. Item 11: Case Report Tabulations (CRT's).

Our filing review is only a preliminary evaluation of the application and is not indicative of deficiencies that may be identified during our review.

If you have any questions, please call Ms. Jena Weber, Regulatory Project Manager, at 301-827-6422.

Sincerely,

{See appended electronic signature page}

Kati Johnson, R.Ph.
Chief, Regulatory Project Management Staff
Division of Metabolic & Endocrine Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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/s/

Jena Weber
2/13/03 12:30:11 PM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-204/S-006

Novartis Pharmaceuticals Corporation
Attention: Carl Schlotfeldt
Associate Director, Drug Regulatory Affairs
One Health Plaza
East Hanover, NJ 07936-1080

Dear Mr. Schlotfeldt:

We have received your supplemental drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following:

Name of Drug Product:	Starlix® (nateglinide) Tablets
NDA Number:	21-204
Supplement number:	S-006
Review Priority Class:	Standard (S)
Date of supplement:	December 19, 2002
Date of receipt:	December 20, 2002

This supplemental application proposes an expanded indication for use in combination with antidiabetic drugs in the thiazolidinedione class.

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on February 18, 2003 in accordance with 21 CFR 314.101(a). If the application is filed, the user fee goal date will be October 20, 2003.

All communications concerning this supplement should be addressed as follows:

U.S. Postal Service/Courier/Overnight Mail:
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Metabolic & Endocrine Drug Products, HFD-510
Attention: Fishers Document Room, 8B45
5600 Fishers Lane
Rockville, Maryland 20857

If you have any questions, call Jena Weber, Regulatory Project Manager, at (301) 827-6422.

Sincerely,

{See appended electronic signature page}

Kati Johnson
Chief, Regulatory Project Management Staff
Division of Metabolic & Endocrine Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Kati Johnson
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