

CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

**APPLICATION NUMBER
21-204**

Correspondence



NDA 21-204-

DISCIPLINE REVIEW LETTER

DEC 18 2000

Novartis Pharmaceuticals Corp.
Attention: Carl Schlotfeldt
Associate Director DRA
59 Route 10 East
East Hanover, NJ 07936

Dear Mr. Schlotfeldt:

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

We also refer to your submissions dated April 18 and December 13, 2000.

Our review of the two safety updates to your application is complete, and we have identified the following deficiencies:

1. The 60 mg dose appears to be not effective in patients with renal impairment. If this is the case, it should be clearly stated in the package insert.
2. The data submitted do not provide any information regarding the efficacy of the 120mg dose in the population with impaired renal function. Provide relevant information to show whether this dose is effective in that population.
3. Although hypoglycemia is the predominant (serious) adverse event based on the April 18, 2000, safety update, hypoglycemia is not mentioned at all in the December 13, 2000, safety update. Provide any missing data or an explanation of its absence from the safety update.

We are providing these comments to you before we complete our review of the entire application to give you preliminary notice of issues that we have identified. In conformance with the prescription drug user fee reauthorization agreements, these comments do not reflect a final decision on the information reviewed and should not be construed to do so. These comments are preliminary and subject to change as we finalize our review of your application. In addition, we may identify other information that must be provided before we can approve this application. If you respond to these issues during this review cycle, depending on the timing of your response, and in conformance with the user fee reauthorization agreements, we may not be able to consider your response before we take an action on your application during this review cycle.

NDA 21-204

Page 2

If you have any questions, call Enid Galliers, Chief, Project Management Staff, at (301) 827-6430.

Sincerely,

/s/

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

facsimile

TRANSMITTAL

to: Mr. Carl Schlotfeldt
fax #: 973-781-3590 (Phone: 973-781-3570)
re: Information request for NDA 21-204 Starlix (nateglinide) Tablets
date: 18 December 2000
pages: 4 3 (including cover page)

A copy of an information request letter is attached.

A hard copy of the letter will also be posted.

THIS DOCUMENT IS INTENDED ONLY FOR THE USE OF THE PARTY TO WHOM IT IS ADDRESSED AND MAY CONTAIN INFORMATION THAT IS PRIVILEGED, CONFIDENTIAL, AND PROTECTED FROM DISCLOSURE UNDER APPLICABLE LAW.

If you are not the addressee, or a person authorized to deliver this document to the addressee, you are hereby notified that any review, disclosure, dissemination, copying, or other action based on the content of this communication is not authorized. If you have received this document in error, please notify us immediately by telephone at 301-827-6430 and return it to us by mail at the address below. Thank you.

Division of Metabolic and Endocrine Drug Products

From the desk of...
Enid Galliers
Chief, Project Management Staff (HFD-510)
DMEDP, ODE II, CDER, FDA
5600 Fishers Lane, Rm 14B-19
Rockville, MD 20857

301-827-6429
Fax: 301-443-9282

E L E C T R O N I C M A I L M E S S A G E

Date: 07-Dec-2000 05:52pm EST
From: carl.schlotfeldt
carl.schlotfeldt@pharma.Novar
Dept:
Tel No:

TO: WEBERJ

(WEBERJ@A1)

Subject: Re: Revised FDA DRAFT LBL for Starlix as of 12/7/00

Confirming receipt on Dec. 7 at 5:50 PM.

Carl Schlotfeldt
Novartis

Redacted

13

pages of trade

secret and/or

confidential

commercial

information

Novartis Pharmaceuticals, Inc.
Attention: Carl Schlotfeldt
Drug Regulatory Affairs
59 Route 10
East Hanover, NJ 07936-1080

29

Fax: 973-781-3590

Reference: NDA 21-204, Starlix (Nateglinide); original submission dated December 17, 1999.

We have completed our review of the clinical and biopharmaceutical sections of your proposed Starlix application, and have the following comments relating to your dissolution profile. We are providing these comments to you before we complete our review of the entire application to give you preliminary notice of issues that we have identified. In conformance with the prescription drug user fee reauthorization, these comments do not reflect a final decision on the information reviewed and should not be construed to do so. These comments are preliminary and subject to change as finalize our review of your application. In addition, we may identify other information that must be provided before we can approve this application. If you respond to these issues during this review cycle, depending on the timing of your response, and in conformance with the user fee reauthorization agreements, we may not be able to consider your response before we take an action on your application during this review cycle.

Dissolution

The dissolution specification of using 6 units (stage 1 testing) is not acceptable to the Agency. We require that 12 units be tested which corresponds with stage 2 testing.

The multipoint dissolution profiles from the data submitted in this application suggest that the tolerance specifications are too loose. The Agency recommends setting the dissolution tolerances at Q = % @ 20 minutes rather than the proposed Q = % @ 30 minutes.

CLEARED FOR FAXING

1/S/
Steven Johnson, Pharm.D.

1/S/
Hae-Young, Ahn, Ph.D.

1/S/ 11-29-00
David G. Orloff, M.D.
Division Director

1/S/ 128/00
Jena Weber, RHPM

**Fax****Attention** Dr. Steve Johnson**Fax no.** (301) 443-9282**Number of pages** 9 including cover page**Date** 15-Dec-00**Concerning** Response to FDA Fax received 14-Dec-00: 2 dissolution questions/Starlix Tablets/pending NDA 21-204

Dear Dr. Johnson,

Reference is made to the FDA fax that was sent to Novartis on 14-Dec-00 which specifies two questions regarding the dissolutions specifications for Starlix Tablets. Reference is also made to the teleconference held on 15-Dec-00 between Novartis representatives (Carl Schlotfeldt, Drug Regulatory Affairs; Donna Kapples and Robert Clark, Drug Regulatory Affairs - Chemistry, Manufacturing and Controls; Richard Schiesswohl, Analytical Research and Development) and FDA representatives (Dr. Steve Johnson and Dr. Hae-Young Ahn).

At this time, Novartis is providing a response to the two dissolution questions as described in the FDA fax received at Novartis on 14-Dec-00.

Question 1:

The dissolution specification of using 6 units (stage 1 testing) is not acceptable to the Agency. We require that 12 units be tested which corresponds with stage 2 testing.

Response 1:

Novartis acknowledges that 12 units should be tested in order to establish dissolution specifications. As per the referenced teleconference, Novartis will test 6 tablets for the release of routine production batches.

As per the referenced teleconference, please find attached the dissolution release results for 190 batches manufactured at the Novartis commercial facility in Stein, Switzerland. These data tables summarize the dissolution release results (average, low, high) for the 60 mg strength and the 120 mg strength. The two strengths are manufactured from the same granulation and therefore the data is applicable to both strengths. Please note that the specifications have been



set based upon having a substantial amount of data. As the data is very consistent, Novartis feels that additional dissolution testing will not help to build additional quality into the product. The dissolution results for commercial batches of the 180 mg strength are not included because the 180 mg strength is not currently provided for in the How Supplied section of the product labeling.

Question 2:

The multipoint dissolution profiles from the data submitted in this application suggest that the tolerance specifications are too loose. The Agency recommends setting the dissolution tolerances at $Q = \boxed{75} \% @ 20$ minutes rather than the proposed $Q = \boxed{80} \% @ 30$ minutes.

Response 2:

Novartis commits to changing the dissolution specification for Starlix Tablets from $Q = \boxed{80} \% @ 30$ minutes to $Q = \boxed{75} \% @ 30$ minutes.

Novartis would like to set up a time later today to further discuss this Novartis response. I can be reached at (973) 781-6929.

Sincerely,

A handwritten signature in cursive script that reads "Donna Kapples".

Donna Kapples
Chemistry, Manufacturing and Controls
Drug Regulatory Affairs

Novartis Pharmaceuticals, Inc.
Attention: Carl Schlotfeldt
Drug Regulatory Affairs
Route 10
East Hanover, NJ 07936-1080

Fax: 973-781-3590

Reference: NDA 21-204, Starlix (Nateglinide); original submission dated December 17, 1999.

We have completed our review of the clinical and biopharmaceutical sections of your proposed Starlix application, and have the following comments relating to the package insert labeling. We are providing these comments to you before we complete our review of the entire application to give you preliminary notice of issues that we have identified. In conformance with the prescription drug user fee reauthorization, these comments do not reflect a final decision on the information reviewed and should not be construed to do so. These comments are preliminary and subject to change as finalize our review of your application. In addition, we may identify other information that must be provided before we can approve this application. If you respond to these issues during this review cycle, depending on the timing of your response, and in conformance with the user fee reauthorization agreements, we may not be able to consider your response before we take an action on your application during this review cycle.

Labeling Comments

Draft

9

_____ pages redacted from this section of
the approval package consisted of draft labeling

Draft
Labeling

CLEARED FOR FAXING

S/

11-22-00

David G. Orloff, M.D.
Division Director

S/
~~11-21-00~~ 11/21/00

Jena Weber, RHPM

Novartis Pharmaceuticals, Inc.
Attention: Carl Schlotfeldt
Drug Regulatory Affairs
59 Route 10
East Hanover, NJ. 07936-1080

Fax: 973-781-3590

Reference: NDA 21-204, Starlix (Nateglinide); original submission dated December 17, 1999.

This OPDRA consult is in response to a request received on September 12, 2000, from the Division of Metabolic and Endocrine Drug Products, to *re-review* the proposed container labels for this application. Furthermore, a new *sample* carton labeling was also submitted for review of possible interventions in minimizing medication errors.

The draft container labels were previously reviewed on April 7, 2000, as part of the proprietary name review. OPDRA recommends the following labeling revisions that might lead to safer use of the product. The Division of Metabolic and Endocrine Drug Products concurs with this recommendation.

We are providing these comments to you before we complete our review of the entire application to give you preliminary notice of issues that we have identified. In conformance with the prescription drug user fee reauthorization, these comments do not reflect a final decision on the information reviewed and should not be construed to do so. These comments are preliminary and subject to change as finalize our review of your application. In addition, we may identify other information that must be provided before we can approve this application. If you respond to these issues during this review cycle, depending on the timing of your response, and in conformance with the user fee reauthorization agreements, we may not be able to consider your response before we take an action on your application during this review cycle.

LABELING, PACKAGING, AND SAFETY RELATED ISSUES:

In the review of the container labels and the sample carton labeling of Starlix, OPDRA has attempted to focus on safety issues relating to possible medication errors and has the following comments, which might minimize potential user error.

A. CONTAINER LABELS (60 mg, 120 mg, & 180 mg)

1. We recommend revising the statement of the strength, _____ to read, "60 mg", since it is evident that 60 mg of nateglinide is contained in each tablet.
2. On the *sample* container label, the picture of a man next to the proprietary name is distracting to the eye and detracts attention away from the proprietary name. The intention may have been to show a man with glycemic control for this antidiabetic drug, but the implication is not obvious. We recommend deleting this picture.

B. SAMPLE CARTON LABELING (120 mg)

See comments under CONTAINER LABELS.

This information was sent to Mr. Schlotfeldt on November 21, 2000.

CLEARED FOR FAXING

DS/ 11-21-00
David G. Orloff, M.D.

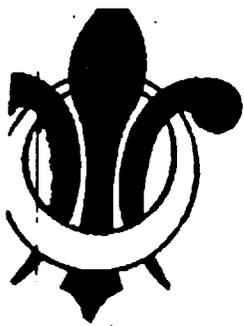
DS/ 11/21/00
Jena Weber, RHPM

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TELEFAX

70.
RE: REWANTS R - DR. Carl Schlotfeldt
RE: NDA 21-209 (Starlix)

FAX: 973-781-3590

PHONE: 3520

FROM: Jena M. Weber, RHPM

FOOD AND DRUG ADMINISTRATION
DIVISION OF METABOLIC AND ENDOCRINE DRUG PRODUCTS
SIX FISHERS LANE, HFD-510

NOV 7 1999

Novartis Pharmaceuticals, Inc.
Attention: Carl Schlotfeldt
Drug Regulatory Affairs
59 Route 10
East Hanover, NJ 07936-1080

Fax: 973-781-3590

Reference: NDA 21-204, Starlix (Nateglinide); original submission dated December 17, 1999.

We have completed our pharmacology/toxicology review this submission, and have the following comments relating to the package insert labeling for this application. We are providing these comments to you before we complete our review of the entire application to give you preliminary notice of issues that we have identified. In conformance with the prescription drug user fee reauthorization, these comments do not reflect a final decision on the information reviewed and should not be construed to do so. These comments are preliminary and subject to change as finalize our review of your application. In addition, we may identify other information that must be provided before we can approve this application. If you respond to these issues during this review cycle, depending on the timing of your response, and in conformance with the user fee reauthorization agreements, we may not be able to consider your response before we take an action on your application during this review cycle.

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 rats approximately 50 times the human therapeutic exposure with a recommended dose of 120 mg, tid. 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 the maximum recommended dose of 120 mg, tid. No evidence of a tumorigenic response was found in either rats and 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 dose of 120 mg, tid.)

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 dose of 120 mg, tid). 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 30 times the human therapeutic exposure with a recommended dose of 120 mg, tid.) There are no adequate and well-controlled studies in pregnant women.

Nursing Mothers:

Studies in lactating rats showed that nateglinide is excreted in the milk; the AUC_{0-48h} ratio in milk to plasma was about 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 dose of 120 mg, tid). 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.

This information was sent to Mr. Schlotfeldt on November 7, 2000.

CLEARED FOR FAXING

ISI 11/7/00
Jeri El-Hage, Ph.D.

ISI 11/7/00
Herman Rhee, Ph.D.

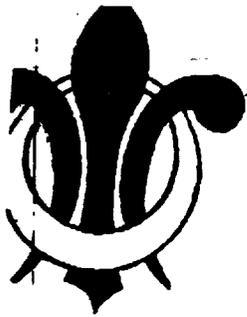
ISI 11/7/00
Jena Weber, RHPM

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TELEFAX

TO: NOVARTIS - DR. Carl Schlotfeldt
REF. NDA 21-209 - PCL LBL

FAX: 973-781-3590

PHONE: 3570

FROM: Jena M. Weber, RHPM

FOOD AND DRUG ADMINISTRATION
DIVISION OF METABOLIC AND ENDOCRINE DRUG PRODUCTS
5600 FISHERS LANE, HHTD-510

Novartis Pharmaceuticals, Inc.
Attention: Carl Schlotfeldt
Drug Regulatory Affairs
59 Route 10
East Hanover, NJ 07936-1080

SEP 11 2000

Fax: 973-781-~~6365~~ 3570

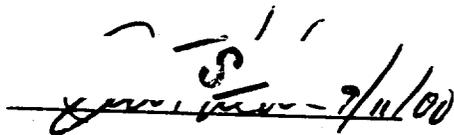
Ref: NDA 21-204

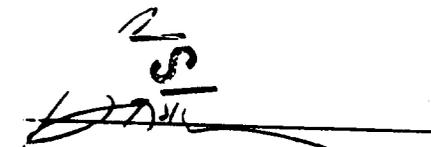
Carl,

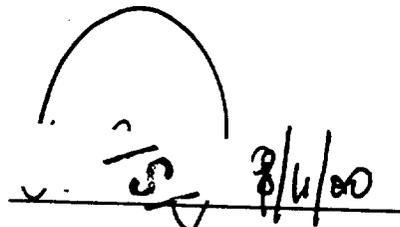
Please see the attached page that includes items we would like clarified. Drs. Koller, Malozowski, and myself will phone you tomorrow (9/12/00) at noon.

Thankyou in advance for your consideration in this matter.

CLEARED FOR FAXING


Jena Weber, CSO


Beth Koller, M.D.


Saul Malozowski, M.D.

- 1—Please identify the studies which had extensions.
- 2--Previously, we had asked for extension data (HgbA1c, Hypoglycemia, Glucose-fasting, Weight), q 12 weeks, at extension end, and LOCF-with a listing of when the person left prematurely if they did so and why. These data were to be on the original diskettes, but were not included.
- 3—Please provide the location for study report 304.
- 4—Please provide: Adverse events $\geq 1\%$ for each of the studies: 202, 251, 302, 351, 354, and 356 and each of the extension studies.
If a pt had more than 1 symptom, would like to know that and the cluster of symptoms.
- 5—Please provide a list of the patients and their study/treatment group with alk phos, GGT, SGPT, and SGOT $\geq 2x$ ULN at entry or exit.
If a pt had more than 1 hepatic enzyme elevation, would like to know that.
What evaluations were done in the patients with elevated levels?
- 6—Please provide a list of the patients and their study treatment group with bilirubin $\geq 1.5 x$ ULN entry or exit.
If a pt had more than 1 hepatic enzyme elevation, would like to know that.
What evaluations were done on patients with elevated bilirubin levels.
- 7--Provide reports on patients with urticaria-hives-pruritis.
- 8--Provide reports on patients who developed sun sensitivity.
- 9—Provide reports on patients with CVAs, CAD, MI, dysrhythmias, ischemia, and congestive failure whether or not it led to discontinuation. Please include the study, treatment group, and whether patients were discontinued and after how much drug exposure.
- 10—Provide reports on the patients with an increase in creatinine $\geq 50\%$.
- 11--Provide reports of patients with uric acid ≥ 1.5 ULN.
- 12—Please provide the definition of clinically significant change in EKG vs not clinically significant. Provide a listing of all patients with significant changes, the nature of change, study, treatment arm, and duration of drug exposure. Include phase 2 studies.
Please provide the location of EKG data and tabulations.
- 13—Provide the location of the table 7.2.-1D with vital signs.
- 14—Provide the narratives of patients who were discontinued for events suggestive of hypoglycemia. p322
- 15--Of those with thirst, polyuria, and polydipsia, nocturia, what was HgnA1c at entry and exit. p295.
- 16—List how many patients were discontinued for GI symptoms and whether they presented with a single symptom or a cluster of symptoms. Include the study, duration of treatment, and treatment arm.

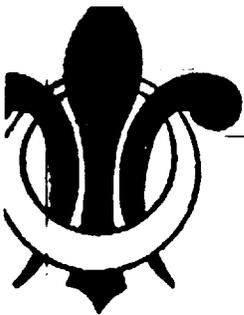
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TELEFAX

TO: NUMBERS Rf - Mr. Carl Schlofeldt

REF. NDA 21-209

FAX: 973-781-3590

PHONE: _____

FROM: Jena M. Weber, RHPM

FOOD AND DRUG ADMINISTRATION
 DIVISION OF METABOLIC AND ENDOCRINE DRUG PRODUCTS
 5600 FISCHER LANE WASHINGTON, DC 20205

NDA 21-204

AUG 15 2000

Novartis Pharmaceuticals Corporation
Attention: Carl Schlotfeldt
Associate Director, Drug Regulatory Affairs
59 Route 10
East Hanover, NJ 07936-1080

Dear Mr. Schlotfeldt:

Reference is made to your correspondence dated March 30, 2000, requesting FDA to issue a Written Request under Section 505A of the Food, Drug, and Cosmetic Act, and requesting a partial waiver pursuant to 21CFR 314.55 for nateglinide.

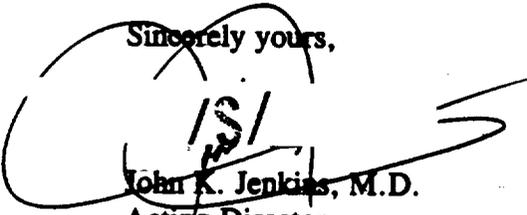
We have reviewed your proposed pediatric study request and are unable to issue a Written Request based on your submission.

Our review of your NDA is still pending, and there is not enough information currently available to adequately issue a Proposed Pediatric Studies Request for this application at this time. Therefore, your request is denied.

We look forward to working with you on this matter in order to develop additional pediatric information that may produce health benefits to the pediatric population.

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

Sincerely yours,



John K. Jenkins, M.D.
Acting Director
Office of Drug Evaluation II
Center for Drug Evaluation and Research

310/Welch

DEC 21 1999

NDA 21-204

Novartis Pharmaceuticals Corporation
Attention: Carl Schlotfeldt
Associate Director, Drug Regulatory Affairs
59 Route 10
East Hanover, NJ 07936-1080

Dear Mr. Schlotfeldt:

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

Name of Drug Product: Starlix® (nateglinide) Tablets, 60, 120, 180 mg

Therapeutic Classification: To be determined at filing meeting

Date of Application: December 17, 1999

Date of Receipt: December 17, 1999

Our Reference Number: NDA 21-204

Unless we notify you within 60 days of our receipt date that the application is not sufficiently complete to permit a substantive review, this application will be filed under section 505(b) of the Act on February 15, 2000, in accordance with 21 CFR 314.101(a). If the application is filed, the primary user fee goal date will be October 17, 2000, and the secondary user fee goal date will be December 17, 2000.

Be advised that, as of April 1, 1999, all applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred (63 FR 66632). If you have not already fulfilled the requirements of 21 CFR 314.55 (or 601.27), please submit your plans for pediatric drug development within 120 days from the date of this letter unless you believe a waiver is appropriate. Within 120 days of receipt of your pediatric drug development plan, we will notify you of the pediatric studies that are required under section 21 CFR 314.55.

If you believe that this drug qualifies for a waiver of the pediatric study requirement, you should submit a request for a waiver with supporting information and documentation in accordance with the provisions of 21 CFR 314.55 within 60 days from the date of this letter. We will notify you within 120 days of receipt of your response whether a waiver is granted. If a waiver is not

granted, we will ask you to submit your pediatric drug development plans within 120 days from the date of denial of the waiver.

Pediatric studies conducted under the terms of section 505A of the Federal Food, Drug, and Cosmetic Act may result in additional marketing exclusivity for certain products (pediatric exclusivity). You should refer to the *Guidance for Industry on Qualifying for Pediatric Exclusivity* (available on our web site at www.fda.gov/cder/pediatric) for details. If you wish to qualify for pediatric exclusivity you should submit a "Proposed Pediatric Study Request" (PPSR) in addition to your plans for pediatric drug development described above. We recommend that you submit a Proposed Pediatric Study Request within 120 days from the date of this letter. If you are unable to meet this time frame but are interested in pediatric exclusivity, please notify the division in writing. FDA generally will not accept studies submitted to an NDA before issuance of a Written Request as responsive to a Written Request. Sponsors should obtain a Written Request before submitting pediatric studies to an NDA. If you do not submit a PPSR or indicate that you are interested in pediatric exclusivity, we will proceed with the pediatric drug development plan that you submit and notify you of the pediatric studies that are required under section 21 CFR 314.55. Please note that satisfaction of the requirements in 21 CFR 314.55 alone may not qualify you for pediatric exclusivity. FDA does not necessarily ask a sponsor to complete the same scope of studies to qualify for pediatric exclusivity as it does to fulfill the requirements of the pediatric rule.

We note your intent to submit a formal plan for the study of Starlix in the pediatric population (age 12 and above) within approximately 3 months.

Please cite the NDA number listed above at the top of the first page of any communications concerning this application. All communications concerning this NDA 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 and Endocrine Drug Products, HFD-510
Attention: Division Document Room, 14B-19
5600 Fishers Lane
Rockville, Maryland 20857

NDA 21-204

Page 3

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

Sincerely,

ISI
2/21/99

Enid Galliers
Chief, Project Management Staff
Division of Metabolic and Endocrine Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research



No. 4841 P. 2
Novartis Pharmaceuticals Corporation
Drug Regulatory Affairs
59 Route 10
East Hanover, NJ 07936-1080

Tel: 973 781 7500
Fax: 973 781 3590

December 22, 2000

David Orloff, MD
Director
Division of Metabolic and
Endocrine Drug Products/HFD-510
Office of Drug Evaluation II
Attn: Document Control Room 14B-19
Center for Drug Evaluation and Research
5600 Fishers
Rockville, Maryland 20857

NDA No. 21-204
Starlix® (nateglinide) Tablets

Dear Dr. Orloff:

Yesterday we discussed several aspects of the draft package insert for Starlix. One of the issues we discussed was whether a statement at the end of the Starlix Combination Therapy/Metformin subsection could be improved to read more clearly.

We are proposing the following revisions in bold text. The current sentence which precedes it is provided for context:

The combination of Starlix and metformin resulted in statistically significantly greater reductions in HbA_{1c} and FPG compared to either Starlix or metformin therapy (Table 2). **Starlix, alone or in combination with metformin, significantly reduced the prandial glucose elevation from pre-meal to 2-hour post-meal compared to placebo and metformin alone.**

Please advise me of your preference so we can proceed with the preparation of our final draft.

If you have any questions concerning this matter, please call me at 973-781-3570.

Sincerely,

Adrian L. Birch
Executive Director
Drug Regulatory Affairs

Submitted in duplicate

DUPLICATE

December 20, 2000



David Orloff, MD
Director
Division of Metabolic and
Endocrine Drug Products/HFD-510
Office of Drug Evaluation II
Attn: Document Control Room 14B-19
Center for Drug Evaluation and Research
5600 Fishers
Rockville, Maryland 20857

NDA No. 21-204
Starlix® (nateglinide) Tablets

Dear Dr. Orloff:

Recently we were advised of additional FDA requested revisions to our draft package insert for Starlix (nateglinide). Among those revisions, we were asked to delete the following sentence which appears in the Metformin paragraph of the Clinical Studies section of our labeling:

As explained to us, an FDA statistical assessment of that statement raised questions concerning the strength of the available data to support it.

We have since performed our own assessment of the data, and we have concluded that there is more than adequate data to support the legitimacy of the statement. We offer the following arguments as a basis for our conclusion:

1. An ANCOVA model showed that the baseline HbA_{1C} effect (covariate) on the change from baseline (response) was highly statistically significant with a p-value < 0.0001, indicating that the baseline HbA_{1C} was a good predictor of the response (change from baseline) since the slope was significantly different from 0. Please refer to attached pages 1 to 6 for additional details.
2. The plot of changes versus baseline with linear regression lines by treatment showed negative slopes for all treatment groups, suggesting that the higher the baseline, the greater the reduction. Please refer to page 7 attached.
3. The summary statistics on changes by baseline HbA_{1C} group clearly demonstrated that the reductions increased as baseline increased in all treatment groups. Please refer to page 8 attached.
4. The Pearson correlation coefficients between change and baseline were -0.5, -0.3, -0.3, -0.2 for the combination, nateglinide, metformin, and placebo, respectively. All of them were statistically significant from 0 (p-values < 0.001 for all active treatment groups), consistently indicating that the higher the baseline, the bigger the reduction. Please refer to pages 9 to 13 attached for additional details.
5. For each treatment group, the linear relationship between baseline and change from baseline in HbA_{1C} can be quantified by estimating the slope using the same ANCOVA model. The slope estimates were -0.47, -0.41, -0.18, and -0.19 for combination, nateglinide, metformin, and placebo, respectively, indicating that for every unit increase in baseline (i.e., 1% increase in baseline HbA_{1C}), the reduction in HbA_{1C} increased 0.47%, 0.41%, and 0.18% for combination, nateglinide, and metformin, respectively. Please refer to pages 14 to 16 attached.

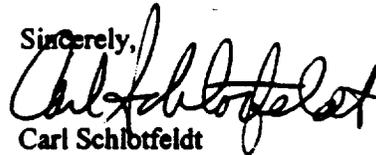
We would like to remind you that the following statements appear in the recently approved labeling for Glucophage (metformin):

"The magnitude of the decline in fasting blood glucose concentration following the institution of GLUCOPHAGE therapy was proportional to the level of fasting hyperglycemia. Patients with type 2 diabetes with higher fasting glucose concentrations experienced greater declines in plasma glucose and glycosylated hemoglobin."

As noted in our Item 4 discussion above, both Starlix and metformin had the same statistically significant correlation coefficients. As discussed in Item 5 above, the linear relationship between baseline and change from baseline indicates a greater reduction in HbA_{1c} for nateglinide as baseline HbA_{1c} increases. We think it is only fair that we be allowed to include a similar statement in the package insert for Starlix. Thus, we urge you to reconsider your position on this matter on the basis of the Starlix data, the equivalent response in metformin patients, and the clear precedent that was established with the recent approval of Glucophage.

If you have any questions concerning this matter, please call me at 973-781-3570.

Sincerely,



Carl Schlotfeldt
Associate Director
Drug Regulatory Affairs

Attachments
Submitted in duplicate



NO. 4815 3 2
Novartis Pharmaceuticals Corporation
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59 Route 10
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Fax 973 781 3590

December 19, 2000

David Orloff, MD
Director
Division of Metabolic and
Endocrine Drug Products/HFD-510
Office of Drug Evaluation II
Attn: Document Control Room 14B-19
Center for Drug Evaluation and Research
5600 Fishers
Rockville, Maryland 20857

NDA No. 21-204
Starlix® (nateglinide) Tablets

Response to Discipline Review Letter

Dear Dr. Orloff:

We refer to our pending NDA 21-204 for Starlix and to the Discipline Review Letter which we received via telefax on December 18, 2000. Your letter contains three questions regarding information contained in the NDA safety updates submitted on April 18 and December 13, 2000.

The following is our response to your questions:

Question 1: The 60 mg dose appears to be not effective in patients with renal impairment. If this is the case, it should be clearly stated in the package insert.

Enclosed is our report entitled "Response to FDA questions Received on December 18, 2000." In Item 2 on pages 10 and 11 of this report there is a further description of the results of protocol 102, in which Starlix was administered to patients with varying degrees of renal impairment. The efficacy results for the 60 mg dose in this study are a result of switching from previous chronic therapy, not a function of renal impairment. This is addressed in currently proposed labeling.

Question 2: The data submitted do not provide any information regarding the efficacy of the 120 mg dose in the population with impaired renal function. Provide relevant information to show whether this dose is effective in that population.

It is our understanding that it is not necessary to document efficacy in special populations. We conducted a pharmacokinetic study in renally impaired patients in accordance with FDA's guidance document on that subject. As reflected in our current draft labeling which has cleared Biopharm review, the results of that study indicated that no dose adjustment is necessary for renally impaired patients.

Attached to this letter is a document which addresses the Starlix 60 mg dose in renally impaired patients (See response to question 1). It correctly notes that patients in Protocol 102 were somewhat abruptly switched from other oral antidiabetic medications to Starlix, and they experienced a subsequent decline in glycemic control. A control group in the same study had similar outcomes, so it is reasonable to conclude that the switching design of the study adversely affected efficacy independent of renal status. Based on our favorable PK results and the extenuating circumstances of the design of Protocol 102, it is reasonable to assume that the Starlix 120 mg dose should be efficacious in renally impaired patients.

Questions 3: Although hypoglycemia is the predominant (serious) adverse event based on the April 18, 2000 safety update, hypoglycemia is not mentioned at all in the December 13, 2000, safety update. Provide any missing data or an explanation of its absence from the safety update.

We agree that hypoglycemia is the predominant adverse event seen in clinical trials with Starlix. However, there were no confirmed reports of serious hypoglycemia in any of our studies (serious hypoglycemia is defined in all our protocols as events requiring the assistance of another person).

David Orloff, MD

NDA No. 21-204

As mentioned in our letter sent to you earlier today in which we described the December 13, 2000 safety update, information in that report is limited (upon instructions from FDA) to patient exposures, serious events and deaths. Since there were no cases of hypoglycemia in the time period covered by that report that met the definition of serious, none are mentioned.

In the attached report entitled "Response to FDA Questions Received on December 18, 2000," we are providing supplementary safety information on hypoglycemia obtained during the reporting period covered by the December 13, 2000 safety update. It consists of the non-serious events reported in the three recently completed trials, studies 103, 116 and 351E02.

If you have questions on the above, please call me at 973-781-3570.

Sincerely,

Carl Schlottfeldt
Associate Director
Drug Regulatory Affairs

Attachments
Submitted in duplicate

 NOVARTIS

COPY 2
DUPLICATE

Novartis Pharmaceuticals Corporation
Drug Regulatory Affairs
59 Route 10
East Hanover, NJ 07936-1080

Tel 973 781 7500
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December 18, 2000



David Orloff, MD
Director
Division of Metabolic and
Endocrine Drug Products/HFD-510
Office of Drug Evaluation II
Attn: Document Control Room 14B-19
Center for Drug Evaluation and Research
5600 Fishers
Rockville, Maryland 20857

NDA No. 21-204
Starlix® (nateglinide) Tablets

Dear Dr. Orloff:

We refer to our pending NDA for Starlix and to the letter we received via telefax on November 21, 2000 from the Division. It includes two comments on container and sample carton labels. A copy is attached.

We agree to delete the picture of a man next to the proprietary name on the sample carton.

We have carefully considered the recommendation in your letter to revise the statement of strength to read 60 mg instead of () Based on our experience, we believe that () is clearer to the reader. Thus, we propose not to revise the statement of strength. This was communicated to Ms. Jena Weber, Project Manager in HFD-510 via telephone on November 22, 2000, and it is our understanding that this was accepted.

Please contact me at 973-781-3570 if you have any questions regarding this matter.

Sincerely,



Carl Schlotfeldt
Associate Director
Drug Regulatory Affairs

Attachment
Submitted in duplicate

Novartis Pharmaceuticals Corporation
Drug Regulatory Affairs
59 Route 10
East Hanover, NJ 07936-1080



Tel 973 781 7500
Fax 973 781 6325



SPJ
12-20-00
IN DFS

18-Dec-00

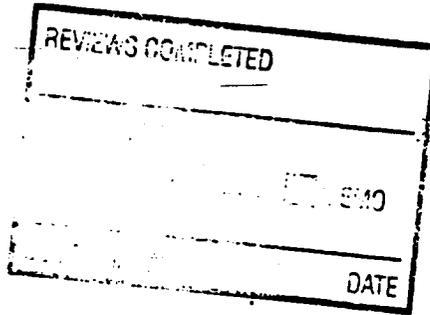
ORIG AMENDMENT

ORIGINAL

NDA 21-204
Starlix® (nateglinide) Tablets

Amendment to pending NDA - Chemistry, Manufacturing and Controls

David Orloff, MD, Director
Division of Metabolic and
Endocrine Drug Products/HFD-510
Office of Drug Evaluation II
Attn: Document Control Room 14B-19
Center for Drug Evaluation and Research
5600 Fishers Lane
Rockville, Maryland 20857



Dear Dr. Orloff:

At this time, Novartis is amending the referenced pending NDA with the information that was faxed to the attention of Dr. Steve Johnson, FDA Division of Biopharmaceutics, on 15-Dec-00. This fax responded to the two dissolution questions received by Novartis from the FDA on 14-Dec-00. Dr. Johnson telephoned Donna Kapples at the end of the day, 15-Dec-00, to inform Novartis that the FDA has accepted the proposal as presented in the attached fax.

Should you have any comments or questions regarding this submission or any other Chemistry, Manufacturing and Controls issue please contact me directly at (973) 781-6929. If there are any general or Clinical related issues please contact Carl Schlotfeldt, the DRA Therapeutic Area representative at (973) 781-3570.

Sincerely,

Donna Kapples
Chemistry, Manufacturing and Controls
Drug Regulatory Affairs

Attachments
Submitted in Duplicate
Cover Letter only: Dr. Steve Johnson, FDA Division of Biopharmaceutics



Novartis Pharmaceuticals Corporation
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59 Route 10
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Tel 973 781 7500
Fax 973 781 3590

December 13, 2000

Ms. Jena Weber
Regulatory Health Project Manager
Division of Metabolic and
Endocrine Drug Products/HFD-510
Office of Drug Evaluation II
Attn: Document Control Room 14B-19
Center for Drug Evaluation and Research
5600 Fishers
Rockville, Maryland 20857

NDA No. 21-204
Starlix® (nateglinide) Tablets

Response to Requests for Information
Additional Desk Copy of 120-Day
Safety Update

Dear Ms. Weber:

As per your telephone request today, enclosed is a desk copy (12 volumes) of the 120-Day Safety Update for Starlix® (nateglinide) NDA 21-204.

If you have any questions or comments, please contact me at (973) 781-3570 (FAX 973-781-3590).

Sincerely,

A handwritten signature in cursive script, appearing to read 'Carl Schlottfeldt'.

Carl Schlottfeldt
Associate Director
Drug Regulatory Affairs

Attachment (12 volumes)

Desk copy: Dr. E. Koller, HFD-510
Ms. J. Weber, HFD-510 (letter only)



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December 13, 2000

—David Orloff, MD
Director
Division of Metabolic and
Endocrine Drug Products/HFD-510
Office of Drug Evaluation II
Attn: Document Control Room 14B-19
Center for Drug Evaluation and Research
5600 Fishers
Rockville, Maryland 20857

NDA No. 21-204
Starlix® (nateglinide) Tablets

Supplementary Safety Update

Dear Dr. Orloff:

Reference is made to our pending NDA 21-204 for Starlix (nateglinide) tablets.

At this time we are responding to a verbal request from Ms. Jena Weber to provide you with a supplementary safety update for our product. As you know, we previously submitted a 120-Day Safety Update on April 18, 2000. The new safety update has been prepared in accordance with the verbal request we received, and it is attached for your reference.

If there is a need to discuss any aspect of our pending application, I can be reached at (973) 781-3570 (FAX 973-781-3590).

Sincerely,

Carl Schlotfeldt
Associate Director
Drug Regulatory Affairs

Attachments
Submitted in duplicate

Desk Copy: E. Koller c/o J. Weber

Novartis Pharmaceuticals Corporation
Drug Regulatory Affairs
59 Route 10
East Hanover, NJ 07936-1080

 **NOVARTIS**

Tel 973 781 7500
Fax 973 781 3590

December 1, 2000

David Orloff, MD
Director
Division of Metabolic and Endocrine
Drug Products/HFD-510
Office of Drug Evaluation II
Attn: Document Control Room 14B-19
Center for Drug Evaluation and Research
5600 Fishers Lane
Rockville, Maryland 20857

NDA No. 21-204
Starlix® (nateglinide) Tablets

Revised Draft Labeling

Dear Dr. Orloff:

Reference is made to our pending NDA 21-204 for Starlix (nateglinide), and to the labeling comments that were forwarded to us last week. We have reviewed those comments, and have difficulty accepting them in their entirety. To facilitate further dialogue on this matter, we are providing you with a revised version of our draft labeling. That version is a comprehensive document which shows our original draft, the comments provided to us, and counter proposals we generated in response to some of those comments. Please be aware that we made fairly extensive use of endnotes to provide you with our perspectives regarding suggested revisions to our labeling.

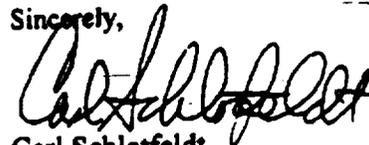
We feel that a meeting would facilitate resolution of any issues which may remain after your review of our re-drafted text. However, we recognize that we are all under significant time constraints to achieve a first action approval by December 15th, and we would be willing to entertain alternate approaches to finalize our labeling. Thus we would like to be advised if, in your opinion, there are equally productive interactions we might arrange to achieve closure with your Division.

We are committed to support you in achieving a first action approval, and we will be prepared to make necessary commitments at our forthcoming meeting.

We are prepared to meet with you at your earliest convenience.

I would appreciate it if you would call me at 973-781-3570 to discuss any aspect of this matter.

Sincerely,



Carl Schlotfeldt
Associate Director
Drug Regulatory Affairs

/kp
Attachment
Submitted in duplicate

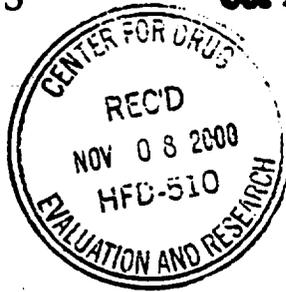
 NOVARTIS

DUPLICATE
ORIG AMENDMENT

COPY 2 *BB*

Novartis Pharmaceuticals Corporation
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59 Route 10
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Tel 973 781 7500
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November 6, 2000

David Orloff, MD, Director
Division of Metabolic and
Endocrine Drug Products/HFD-510
Office of Drug Evaluation II
Attn: Document Control Room 14B-19
Center for Drug Evaluation and Research
5600 Fishers
Rockville, Maryland 20857

NDA No. 21-204
Starlix® (nateglinide) Tablets

Response to FDA Request for Information

Dear Dr. Orloff:

We refer to our pending NDA 21-204 for Starlix tablets. We also refer to a telephone request from Dr. Steven Johnson, Biopharmaceutics Reviewer on Thursday, November 2, 2000. At that time we were asked to provide dissolution test results for 6 additional tablets representative of FMI-2, 120 mg batch H-05226.

The attached table 1 lists the individual test results for a total of 12 tablets from batch H-05226. This is an addendum to the report filed via NDA amendment dated October 20, 2000, entitled:

"Nateglinide 60 mg, 120 mg, 180 mg tablets Dissolution performance individual data,"
dated 18 October 2000.

If you have any questions or comments regarding this submission, please call me at (973) 781-3570.

Sincerely,

Carl Schlotfeldt
Associate Director
Drug Regulatory Affairs

Attachments
Submitted in duplicate
Desk copy: Dr. S. Johnson, HFD-510



Novartis Pharmaceuticals Corporation
Drug Regulatory Affairs
59 Route 10
East Hanover, NJ 07936-1080

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November 1, 2000

David Orloff, MD, Director
Division of Metabolic and
Endocrine Drug Products/HFD-510
Office of Drug Evaluation II
Attn: Document Control Room 14B-19
Center for Drug Evaluation and Research
5600 Fishers
Rockville, Maryland 20857

NDA No. 21-204
Starlix® (nateglinide) Tablets

Response to Requests for Information

Dear Dr. Orloff:

We refer to our pending NDA 21-204 for Starlix (nateglinide). We also refer to telephone requests from Dr. E. Koller, Medical Review Officer received on Friday, October 13 and on Wednesday, October 18, 2000.

On October 13 we were asked to provide reformatted tables of adverse events (incidence $\geq 1\%$) so that similar body system terms would be grouped together. Via our previous amendment dated October 23, 2000 we provided reformatted tables for 7 phase 3 trials. Herein in Attachment 1, we are providing reformatted tables 10.1-2a for the 4 phase 2 trials (B202, core and extension and B251 core and extension).

Please note that for B202 extension the tables were run for a) the overall population, b) for patients taking concomitant metformin and c) for patients not receiving metformin.

We were also asked to provide tables showing the number (and percent) of patients reporting one, two, three, etc. AEs, or AE symptoms for phase 2 and 3 clinical trials. Similar tables for symptoms suggestive of hypoglycemia were also requested. These were provided for the phase 3 trials via the previous amendment dated October 23, 2000. Herein, in Attachments 2 and 3 we are providing Table 3 (AEs and AE symptoms) and Table 3A (symptoms suggestive of hypoglycemia) for phase 2 protocols B202 and B251 (core and extension).

Please note that for B202 extension, these tables were run for a) the overall population, b) for patients taking metformin concomitantly, and c) for patients not receiving metformin.

On October 18 we were asked to provide the insulin profiles for patients in protocol B355, for which we had previously provided glycemic parameter data on diskette (see NDA amendment dated April 20, 2000). Enclosed in Attachment 4 is a replacement diskette for protocol B355 which includes both glycemic and insulin data for each patient. It has been scanned for viruses using Viruscan software.

If you have any questions or comments on the above, please contact me at (973) 781-3570 (FAX 973-781-3590).

Sincerely,

Carl Schlötfeldt
Associate Director
Drug Regulatory Affairs

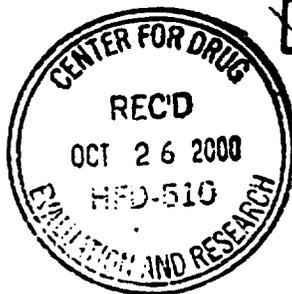
Attachments

Submitted in duplicate

Desk copy: Dr. E. Koller, HFD-510

Ms. J. Weber, HFD-510 (letter only)

 **NOVARTIS**



DUPLICATE
ORIGINAL AMENDMENT
93M

Novartis Pharmaceuticals Corporation
Drug Regulatory Affairs
Route 10
East Hanover, NJ 07936-1080

Tel 973 781 7500
Fax 973 781 3590

October 23, 2000

David Orloff, MD, Director
Division of Metabolic and
Endocrine Drug Products/HFD-510
Office of Drug Evaluation II
Attn: Document Control Room 14B-19
Center for Drug Evaluation and Research
5600 Fishers
Rockville, Maryland 20857

NDA No. 21-204
Starlix® (nateglinide) Tablets

Response to FDA Request
for Information

Dear Dr. Orloff:

We refer to our pending NDA 21-204 for Starlix. We also refer to a telephone request from Dr. E. Koller, Medical Review Officer received on Friday, October 13, 2000. This was in response to our NDA amendment dated October 4, 2000, item 4.

We were asked to reformat Post Text Tables 10.1-2 for protocols B302, B304, B351, B351E01, B354, B355 and B356 so that similar body system terms are grouped together. We were also asked to provide Tables 3 and 3a (clusters of AEs/AE symptoms and clusters of symptoms suggestive of hypoglycemia) for the controlled clinical trials in accordance with the presentation concepts we provided in the October 4 amendment.

Enclosed in Attachment 1 are the reformatted Post Text Tables 10.1-2 for the seven referenced trials.

Enclosed in Attachment 2 are the tables 3 for each of the seven phase 3 trials.

Enclosed in Attachment 3 are the tables 3a for each of the seven phase 3 trials.

If you have any questions or comments regarding the contents of this submission, please call me at (973) 781-3570.

Sincerely,

Carl Schlotfeldt
Associate Director
Drug Regulatory Affairs

Attachments
Submitted in duplicate
Desk copy: Dr. E. Koller, HFD-510

DUPLICATE
DRUG AMENDMENT

 **NOVARTIS** BB



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October 20, 2000

David Orloff, MD, Director
Division of Metabolic and
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Office of Drug Evaluation II
Attn: Document Control Room 14B-19
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5600 Fishers
Rockville, Maryland 20857

NDA No. 21-204
Starlix® (nateglinide) Tablets

Response to FDA Request for Information

Dear Dr. Orloff:

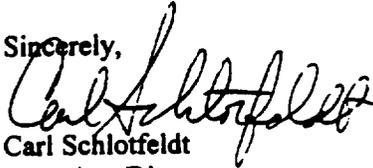
We refer to our pending NDA 21-204 for Starlix tablets. We also refer to a telephone request from Dr. Steven Johnson, Biopharmaceutics Reviewer on Monday, October 16, 2000. At that time we were asked to provide dissolution test results for the individual tablets representative of all strengths, both FMI and phase 3 formulations.

Attached is a report entitled:

"Nateglinide 60 mg, 120 mg, 180 mg tablets Dissolution performance individual data,"
dated 18 October 2000.

If you have any questions or comments regarding this submission, please call me at (973) 781-3570.

Sincerely,


Carl Schlotfeldt
Associate Director
Drug Regulatory Affairs

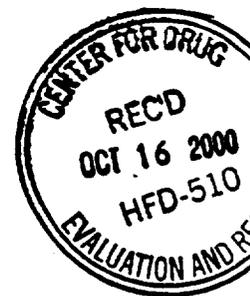
Attachments
Submitted in duplicate
Desk copy: Dr. S. Johnson, HFD-510

 NOVARTIS

DUPLICATE

ORIG AMENDMENT

BM October 13, 2000



David Orloff, MD
Director
Division of Metabolic and
Endocrine Drug Products/HFD-510
Office of Drug Evaluation II
Attn: Document Control Room 14B-19
Center for Drug Evaluation and Research
5600 Fishers
Rockville, Maryland 20857

NDA No. 21-204
Starlix® (nateglinide) Tablets

Response to FDA Request
For Information

Dear Dr. Orloff:

We refer to our pending NDA 21-204 Starlix. We also refer to the request for additional clinical information we received from the Division via telefax on September 12, 2000 and to our previous NDA amendments dated September 21, 2000, October 4, 2000 and October 10, 2000 which were submitted in partial response to the request. Previously we have addressed items 1 through 4, and items 7 through 16 of the request for information. The following is our response to items 5 and 6.

Item 5 - Please provide a list of the patients and their study/treatment group with alkaline phosphatase, GGT, SGPT, and SGOT $\geq 2X$ ULN at entry or exit. If a patient had more than 1 hepatic enzyme elevation, we would like to know that. What evaluations were done in the patients with elevated levels?

Item 6 - Please provide a list of the patients and their study treatment group with bilirubin $> 1.5X$ ULN at entry or exit. If a patient had more than 1 hepatic enzyme elevation, we would like to know that. What evaluations were done in the patients with elevated levels?

Response: Attachment 1 is a listing of patients with >2 ULN abnormalities for laboratory tests for Gamma GT, SGPT, SGOT, alkaline phosphatase or >1.5 ULN for total bilirubin at study entry or exit (all completed trials in the NDA safety database). The listing is organized by protocol (starting with B202) and by treatment group (starting with nateglinide) within each protocol. It includes information on patient age, sex, race, height and weight. If a patient had more than one hepatic enzyme elevation and/or elevation in total bilirubin, all relevant tests are displayed for each patient. For each test for which a patient had an abnormality, all values for that test obtained during the patient's participation in the trial are displayed. For each lab value, information on the visit day, visit number, visit day (relative to randomization), study drug dose at visit, the actual lab value and the upper limit of normal are displayed.

In the clinical trials that contributed data to the pooled NDA safety database, there were no prespecified evaluations that were to be conducted if a patient had an abnormal safety lab test result. All follow-ups, including repeat labs, were to be done at the discretion of the

investigator. Results of retests ordered by the investigator are designated in Attachment 1 by the letter "R".

Review of the premature discontinuation and adverse event listings revealed no evaluations conducted in these patients beyond the repeat laboratory tests contained within attachment 1. This review did identify 9 patients who had adverse events recorded that are potentially related to these increases in liver function tests or who discontinued from a trial prematurely for a laboratory finding. This information on these 9 patients is displayed below.

Trial ID	Patient ID	Adverse Event/Reason for Trial Discontinuation	Action Taken	Causality*
Treatment: Nateglinide				
B302	0320008	Hepatitis	None	related
B304	0460009	Increase in LFTs	Premature trial discontinuation	NA**
Treatment: Nateglinide + Metformin				
B354	0620002	Hepatic metastases of pancreatic cancer	Premature trial discontinuation	No
B354	0710005	Increased CPK (adverse reaction to cerivistatin)	Premature trial discontinuation	NA**
Treatment: Glyburide				
B304	0270010	Hepatocellular damage	None	No
B304	0270014	Hepatocellular damage	None	No
Treatment: Placebo				
B302	014003	Acute hepatitis A	Premature trial discontinuation; patient subsequently died post-study	Yes
B351	0660009	Hepatomegaly	None	No
B351	0770005	Hepatic enzymes increased	Premature trial discontinuation	Yes

*Relationship to study medication as assessed by investigator

**Laboratory abnormality listed as reason for discontinuation on end of study CRF; no corresponding event recorded on adverse event CRF and causality assessment not made.

We have responded to all 16 items in your request. We acknowledge the feedback we received from the medical reviewer (Dr. Koller) via telephone today, concerning the adequacy of the presentation concepts (contained in the October 4 letter) on clusters of symptoms in response to item 4 of the request. We will provide the information as discussed (attachments 2 and 3 of the October 4 amendment) for all the phase 3 trials, including B304 and B355.

If you have any questions or comments regarding this or previous submissions please call me at (973)781-3570 (FAX - (973)781-3590).

Sincerely,



Carl Schlotfeldt
Associate Director
Drug Regulatory Affairs

/cs
Attachment
Submitted in duplicate
Desk Copy: Dr. E. Koller c/o Ms. J. Weber, HFD-510

ORIGINAL
ORIG AMENDMENT
NOVARTIS *BM*



Novartis Pharmaceuticals Corporation
Drug Regulatory Affairs
59 Route 10
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Tel 973 781 7500
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October 10, 2000

David Orloff, MD, Director
Division of Metabolic and
Endocrine Drug Products/HFD-510
Office of Drug Evaluation II
Attn: Document Control Room 14B-19
Center for Drug Evaluation and Research
5600 Fishers
Rockville, Maryland 20857

NDA No. 21-204
Starlix® (nateglinide) Tablets

Response to FDA Request
for Information

Dear Dr. Orloff:

We refer to our pending NDA 21-204 for Starlix. We also refer to the request for additional clinical information we received from the Division via telefax on September 12, 2000 and to our previous NDA amendments dated September 21, 2000 and October 4, 2000 which were submitted in partial response to the request. Previously we have addressed items 1 through 4, and items 10 through 16 of the request for information. The following is our response to items 7 through 9.

Item 7 – Provide reports of patients with urticaria-hives-pruritus.

Response - Attachment 1 is the listing of patients with urticaria-hives-pruritus (all clinical trials in the NDA safety database) by treatment group. It includes information on patient age, race, sex, BMI, the preferred term, seriousness, severity, drug relationship, action taken, and event duration.

Item 8 – Provide reports on patients who developed sun sensitivity.

Response – Attachment 2 is the listing of patients with sun sensitivity (all clinical trials in the NDA safety database). It includes information on patient age, race, sex, BMI, the preferred term, seriousness, severity, drug relationship, action taken, and event duration. Only 2 cases were reported and in both the treatment group was nateglinide.

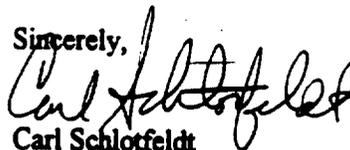
Item 9 – Provide reports on patients with CVAs, CAD, MI, dysrhythmias, ischemia, and congestive heart failure whether or not it led to discontinuation. Please include the study, treatment group, and whether patients were discontinued and after how much drug exposure.

Response – Attachment 3 is the listing of patients with CVAs, CAD, MI, dysrhythmias, ischemia, and congestive heart failure (all clinical trials in the NDA safety database) by treatment group. It includes information on patient age, race, sex, BMI, the preferred term, seriousness, severity, drug relationship, action taken, event duration, whether the patient discontinued and the duration of drug exposure.

We are still in the process of identifying patients and analyzing the information in response to items 5 and 6 of the FDA request. We plan to submit the results of this effort in approximately one week, at which time we will have responded to all 16 items in the request. Also, as indicated in our previous letter dated October 4, 2000, we await your feedback on the adequacy of the presentation concepts (contained in the October 4 letter) on clusters of symptoms in response to item 4 of the request.

If you have any questions or comments regarding this or the previous submissions please call me at (973) 781-3570 [FAX 973-781-3590].

Sincerely,



Carl Schlotfeldt
Associate Director
Drug Regulatory Affairs

Attachments
Submitted in duplicate

Desk copy: Dr. E. Koller c/o Ms. J. Weber, HFD-510

REVIEWS COMPLETED	
CSO ACTION:	
<input type="checkbox"/> LETTER	<input type="checkbox"/> N.A.I. <input type="checkbox"/> MEMO
CSO INITIALS	DATE

 NOVARTIS

ORIGINAL

ORIG AMENDMENT

BM



October 4, 2000

David Orloff, MD, Director
Division of Metabolic and
Endocrine Drug Products/HFD-510
Office of Drug Evaluation II
Attn: Document Control Room 14B-19
Center for Drug Evaluation and Research
5600 Fishers
Rockville, Maryland 20857

NDA No. 21-204
Starlix® (nateglinide) Tablets

Response to FDA Request
for Information

Dear Dr. Orloff:

We refer to our pending NDA 21-204 for Starlix and to the list of questions received on September 12, 2000 from the Division (see Attachment 1). The questions were discussed via teleconference (Drs. Malozowski and Koller and Ms. Weber) that same day. We agreed to furnish the information as soon as items or groups of items are complete. Most of the information and documentation requested is contained in this amendment or was provided in our previous amendment dated September 21, 2000. The balance will be provided in approximately one week.

Item 1 – Please identify the studies which had extensions.

Response – Included in the NDA are data from long term extensions for 3 clinical trials, protocols B202 B251 and B351. The extension portion of the trial is identified with the “E01” suffix to the protocol number, i.e. B202E01, B251E01 and B351E01. Reports for the extension trials are located in NDA, beginning in volumes 255, 294 and 264, respectively.

Item 2 – Previously we had asked for extension data (HbA1c, Hypoglycemia, Glucose-fasting, Weight) at 12 weeks, at extension end and LOCF – with a listing of when the person left prematurely if they did so and why. These data were to be on the original diskettes, but were not included.

Response – Via FDA telefaxes dated February 7 and 26, 2000, we were asked to provide data on diskette for the core and extension phases in protocols B202 and B351. These data (on diskette) were submitted via NDA amendments dated March 17 and 31, 2000 respectively. The electronic datasets were prepared according to instructions contained in the FDA telefax dated February 26, 2000. Subsequently, on July 17, 2000 we submitted a replacement diskette with the data for protocol B351 to make a correction for the derived variable NAIVE only. Data from the extension portion of this trial was inadvertently omitted in the replacement file.

As discussed during the FDA teleconference on September 12, and in a subsequent telephone contact with the Medical Review Officer that same day, we agreed to provide the data from protocol B251 (core and extension) on diskette and a replacement diskette with the data from protocol B351 (core and extension). These were submitted via NDA amendment dated September 21, 2000. The extension data on these diskettes is formatted as specified in FDA telefaxes dated February 26, 2000 and September 12, 2000. Please note that there were no cases of severe hypoglycemia (glucose \leq 36 mg/dl and requiring third party assistance) in either trial and there were no cases of hypoglycemia (glucose \leq 36 mg/dl) in protocol B251.

Item 3 – Please provide the location for study report 304.

Response – The report for protocol B304 can be found beginning in volume 272 of our original NDA (this location is also referenced in the NDA overall index – see vol. 1, page 28 in the original NDA).

Item 4 – Please provide: Adverse events $\geq 1\%$ for each of the studies 202, 251, 302, 351, 354 and 356 and each of the extension studies. If a patient had more than 1 symptom, would like to know that and the cluster of symptoms.

Response – We re-ran post text table 10.1-2a for the phase 3 protocols B302, B351 (core and extension), B354 and B356, using the cutoff of $\geq 1\%$ (we had originally used the cutoff of $\geq 2\%$ for post text table 10.1-2a in the original reports contained in the NDA). These new tables are located in Attachment 2.

Accompanying the report for each of the phase 2 trials in the NDA is a table of all adverse with no cutoff (we refer to it as post text table 10.1-1). Due to the relatively small sample sizes in the phase 2 trials (fewer than 100 patients per group) just a single occurrence of an event exceeds 1%. For this reason we believe that the post-text table 10.1-1 provides the information requested. The NDA locations are as follows:

Protocol	Post-Text Table 10.1-1 (NDA vol/page)
B202 Core	Vol. 200, page 8-1.10 (first page)
B202 Extension	Vol. 255, page 8-212
B251 Core	Vol. 281, page 8-129
B251 Extension	Vol. 295, page 8-204

During our teleconference on September 12, it was agreed that there is no NDA guideline for displaying and analyzing “clusters” of symptoms of adverse events. It was therefore agreed that Novartis would choose an appropriate means of displaying the prevalence of clusters of events or event symptoms across treatment groups and submit an example from one trial. We also agreed to separately display the data collected on symptoms suggestive of hypoglycemia in this manner. Attachment 3 to this letter contains examples of two tabular displays of the number and percent of patients who reported single and multiple events or event symptoms within each body system for protocol B351 (they are entitled, Additional table 3 and Additional table 3a). In table 3, the frequency distribution of single and multiple events or event symptoms (number of patients reporting 1, 2, 3, etc.) is displayed by body system and by treatment group. In table 3a, the frequency distribution of single and multiple symptoms suggestive of hypoglycemia (number of patients reporting 1, 2, 3, etc. symptoms suggestive of hypoglycemia) is displayed by treatment group. We believe that these new tables allow one to assess the prevalence of clusters (of events and event symptoms within a body system and clusters of symptoms suggestive of hypoglycemia) across treatment groups. However, we need confirmation from you that our presentation concept is acceptable before we run similar tables for the other trials.

Item 5 through 9 - Novartis Pharmaceuticals is currently in the process of generating and evaluating the individual patient data and information requested for items 5 through 9 in the telefax. We plan to submit our response to these items in approximately one week.

Item 10– Provide reports on the patients with an increase in creatinine $\geq 50\%$.

Response – Attachment 4 is the listing of patients with an increase in creatinine > 50 (all completed clinical trials in the NDA safety database) by treatment group. It includes information on patient age, race, sex, height and weight, and includes all creatinine values by visit week. This listing is part of the ISS Post text listing 6.1-1 in NDA volume 307 beginning on page 388.

Item 11 - Provide reports of patients with uric acid ≥ 1.5 ULN.

Response - Attachment 5 is a listing of patients with specified percent change from baseline in uric acid (all completed trials in the NDA safety database). Included among these are all patients who had an increase of more than 50% above their baseline value. Sixty-six patients met the >50% criterion from among all completed trials (and all treatment groups) in the NDA safety database. Those that also exceed the upper limit of normal (36 patients across all treatments) are flagged. This is how these data were analyzed in the NDA. The listing includes information on patient age, race, sex, height and weight, and also includes all uric acid values (and % change) by visit week. This listing is part of the ISS Post text listing 6.1-1 in NDA volume 307 beginning on page 352.

Item 12 - Please provide the definition of clinically significant change in ECG vs not clinically significant. Provide a listing of all patients with significant changes, the nature of change, study, treatment arm, and duration of drug exposure. Include phase 2 studies. Please provide the location of the ECG data and tabulations.

Response - In all of the phase 2 and 3 clinical trials, ECG data was collected for all patients. In phase 2 trials, ECGs are classified as normal or abnormal. In phase 3 trials, ECGs are classified as normal, insignificant abnormal or significant abnormal. In all cases, the classification of ECGs as normal, abnormal, clinically significantly abnormal, etc. was based on judgment of the reader. In phase 2 trials, ECGs were read by the investigator. For all phase 3 protocols, a single cardiologist at a central facility read all ECGs for consistency.

The listing of all newly occurring or worsening ECG abnormalities, by protocol, treatment group and patient number for all completed clinical trials in the NDA safety database is contained in Attachment 6. The NDA location for this listing is volume 309 page 8-41. The listing includes information on patient age, race, sex, BMI, and also includes information on duration of drug exposure (in weeks) and the nature of the ECG abnormality. Tabulations of ECG data are also included in the data tabulations section of the NDA (see original NDA Section 11, submitted electronically).

Item 13 - Provide the location of the table 7.2-1D with vital signs.

Response - This table can be found in volume 307 of the original NDA, beginning on page 8-63.

Item 14 - Provide narratives of patients who were discontinued for events suggestive of hypoglycemia.

Response - Narrative descriptions for patients who discontinued [from all clinical and clinical pharmacology trials] for events suggestive of hypoglycemia are contained in Attachment 7.

Item 15 - Of those with thirst, polyuria, and polydipsia, nocturia, what was the HbA_{1c} at entry and exit?

Response - Attachment 8 is a listing of these patients (among all completed studies in the NDA safety database) along with their HbA_{1c} values at entry and exit. No patients were discontinued due to polydipsia.

Item 16 - List how many patients were discontinued for GI symptoms and whether they presented with a single symptom or a cluster of symptoms. Include the study, duration of treatment and treatment arm.

Response - Attachment 9 is a listing of patients who discontinued for GI symptoms (among all completed studies in the NDA safety database) with information on multiple G.I. symptoms (or events) if there was more than one.

As indicated above, for items 5-9 we plan to provide the requested information in approximately one week. Also, as indicated in the response to item 4 above, we await your feedback on the adequacy of the presentation concepts on clusters of symptoms (see Attachment 3).

If you have any questions or comments regarding this submission please call me at (973) 781-3570 [FAX 973-781-3590].

Sincerely,



Carl Schlotfeldt
Associate Director
Drug Regulatory Affairs

Attachments (3 volumes)
Submitted in duplicate

Desk copy: Dr. E. Koller c/o Ms. J. Weber, HFD-510

REVIEWS COMPLETED	
CSO ACTION:	
<input type="checkbox"/> LETTER	<input type="checkbox"/> N.A.I. <input type="checkbox"/> MEMO
CSO INITIALS	DATE

 NOVARTIS

DUPLICATE

BM

Novartis Pharmaceuticals Corporation
Drug Regulatory Affairs
59 Route 10
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Tel 973 781 7500
Fax 973 781 6325

September 21, 2000



David Orloff, MD
Director
Division of Metabolic and
Endocrine Drug Products/HFD-510
Office of Drug Evaluation II
Attn: Document Control Room 14B-19
Center for Drug Evaluation and Research
5600 Fishers
Rockville, Maryland 20857

NDA No. 21-204
Starlix® (nateglinide) Tablets

Response to FDA Request
for Information

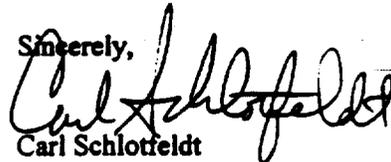
Dear Dr. Orloff:

We refer to our pending NDA 21-204 for Starlix (nateglinide) and to the teleconference with Drs. Malizowski and Koller and Ms. Weber in the Division which took place on September 12, 2000. At that time Novartis was asked to provide data in electronic form for protocol B251 (core and extension). In a subsequent telephone contact with Dr. Koller, we agreed to also submit a replacement electronic dataset for protocol B351 (core and extension).

Accordingly, attached are the electronic datasets for protocols B251 and B351 on diskette. The data is formatted in accordance with specifications which were provided to us by the Division via telefaxes dated February 26, 2000 and September 12, 2000. These files have been scanned and found free of viruses using a program called VirusScan version 4.0.3a by Network Associates Inc.

If you have any questions or comments on the above, I can be reached at 973-781-3570 (FAX 973-781-3590).

Sincerely,



Carl Schlotfeldt
Associate Director
Drug Regulatory Affairs

CS/kp
Attachments
Submitted in duplicate
Desk Copy: Dr. E. Koller, c/o Ms. J. Weber, HFD-510

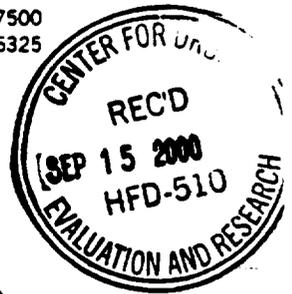
 NOVARTIS

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September 13, 2000

NDA No. 21-204
Starlix® (nateglinide) Tablets

Draft Labeling

David Orloff, MD, Director
Division of Metabolic and
Endocrine Drug Products/HFD-510
Office of Drug Evaluation II
Attn: Document Control Room 14B-19
Center for Drug Evaluation and Research
5600 Fishers
Rockville, Maryland 20857

Dear Dr. Orloff:

Reference is made to our pending NDA for Starlix® (nateglinide). As you are aware, the User Fee goal for the NDA was recently shifted from October 17, 2000 to December 17, 2000 because of workload considerations in the Division. We would like to use this opportunity to introduce new draft labeling for your consideration before we are within 90 days of the action date.

Earlier this year we received separate requests from the medical and statistical reviewers for this NDA to reformat our data on the basis of treatment naive and previously treated patients. Those inquiries prompted our review of the data based on those parameters and led us to conclude that the glycemic effects of Starlix are somewhat greater in treatment naive patients. We recognized that a similar precedent exists with an approved drug for Type II diabetes, and we elected to redraft our labeling to be consistent with that precedent (see Clinical studies section). Please note that we discussed this concept in general terms with Dr. E. Koller and Ms. J. Weber on August 14, 2000.

Given your own interest in this issue, we feel our proposal could facilitate labeling negotiations and approval, which we hope will occur on the revised action date. A summary of our analyses by prior treatment is provided in a report in Attachment A, and our revised draft labeling is provided in Attachment B (hard copy and diskette - scanned for viruses using "Viruscan").

Please note that the revised draft labeling contains a limited number of text revisions in addition to the new information on glycemic effects by prior treatment. In the process of reviewing the draft labeling we noticed several transcription errors, and they have now been corrected. In a few instances the location or the description of the reference had to be corrected as well. Also, in the Adverse Reactions section we have revised the description of lipid elevations in order to express the changes in the context of those which are outside the normal range. We believe this is a more informative description than simply change from baseline. All changes are highlighted.

In that this submission is being made more than 90 days before the projected action date, it is our understanding that it does not provide a basis to implement an extension of the review clock for this NDA.

If you have any questions about this submission please call me at (973) 781-3570.

Sincerely,



Carl Schlotfeldt
Associate Director
Drug Regulatory Affairs

Attachments

Submitted in duplicate

Desk Copy: Dr. E. Koller, HFD-510

Dr. J. Mele, Statistician c/o HFD-510

 NOVARTIS

September 6, 2000

NDA 21-204
Starlix® (nateglinide) Tablets

Amendment to pending NDA - Chemistry, Manufacturing and Controls

John Jenkins, MD, Acting Director
Division of Metabolic and
Endocrine Drug Products/HFD-510
Office of Drug Evaluation II
Attn: Document Control Room 14B-19
Center for Drug Evaluation and Research
5600 Fishers Lane
Rockville, Maryland 20857

Dear Dr. Jenkins:

At this time, Novartis is amending the referenced pending NDA to provide draft labeling (including artwork) for the immediate bottle container (trade and sample) and draft labeling (including artwork) for the carton of the sample bottle container.

Reference is made to a telephone conversation held on 29-Aug-00 between Ms. Jena Weber, FDA Project Manager, and Mr. Carl Schlotfeldt, Novartis DRA Therapeutic Area representative. Ms. Weber requested that Novartis provide immediate container labeling with artwork. The attached draft labeling, including artwork, is being submitted for review. Please note that this submission contains the draft labeling (including artwork) for the carton of the sample bottle container which had not been previously provided to this NDA in text format.

Should you have any comments or questions regarding this submission or any other Chemistry, Manufacturing and Controls issue please contact me directly at (973) 781-6929. If there are any general or Clinical related issues please contact Carl Schlotfeldt, the DRA Therapeutic Area representative at (973) 781-3570.

Sincerely,



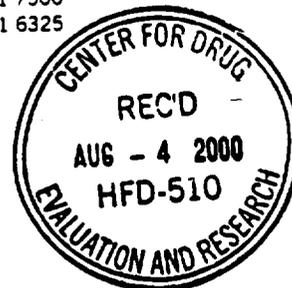
Donna Kapples
Chemistry, Manufacturing and Controls
Drug Regulatory Affairs

 NOVARTIS

ORIGINAL

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59 Route 10
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03-Aug-00

BC

ORIG AMENDMENT

NDA 21-204

Starlix® (nateglinide) Tablets

Amendment to pending NDA - Chemistry, Manufacturing and Controls

John Jenkins, MD, Acting Director
Division of Metabolic and
Endocrine Drug Products/HFD-510
Office of Drug Evaluation II
Attn: Document Control Room 14B-19
Center for Drug Evaluation and Research
5600 Fishers Lane
Rockville, Maryland 20857

Dear Dr. Jenkins:

Reference is made to our pending Starlix Tablets NDA 21-204. At this time, we are amending the NDA to provide a stability report which includes — month real time data for our registration stability batches.

Additional reference is made to a telephone discussion that Dr. Ysern, FDA reviewing chemist, and I had on July 26, 2000. As Dr. Ysern and I discussed, the provision of updated stability data at this time will not have an impact on the action date for this NDA.

The following stability report is provided:

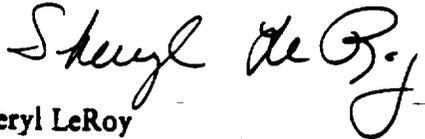
- DJN608 (Nateglinide, Starlix) 60, 120 and 180 mg tablets - Registration Stability Report, RSR6005C.01, dated July 26, 2000

The — month primary stability data continue to show that Starlix Tablets are stable in all three types of packaging. No significant decrease in the assay of nateglinide nor increase in degradation was observed after — months long-term storage at —. There was also no significant change in the dissolution rate of tablets stored under these storage conditions. The — month stability data from the production batches, also included in the attached report, confirm the results from the primary stability batches. Both the — month primary stability data and the — month production stability data support the proposed — month year expiration period for nateglinide tablets.

Should you have any comments or questions regarding this submission or any other Chemistry, Manufacturing and Controls issue please contact me directly at (973) 781-2735. If there are any

general or Clinical related issues please contact Carl Schlotfeldt, the DRA Therapeutic Area representative at (973) 781-3570.

Sincerely,



Sheryl LeRoy
Chemistry, Manufacturing and Controls
Drug Regulatory Affairs

Attachments
Submitted in Duplicate

cc: Ms. Regina Brown
New Jersey District Office, North Brunswick Resident Post - Certified Field Copy



TOTU



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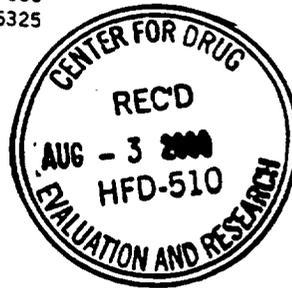
 **NOVARTIS**

**ORIGINAL
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BC

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August 2, 2000

NDA 21-204
Starlix® (nateglinide) Tablets

NDA Amendment - Chemistry, Manufacturing and Controls

John Jenkins, MD
Acting Director
Division of Metabolic and
Endocrine Drug Products/HFD-510
Office of Drug Evaluation II
Attn: Document Control Room 14B-19
Center for Drug Evaluation and Research
5600 Fishers Lane
Rockville, Maryland 20857

Dear Dr. Jenkins:

Please refer to our above-referenced New Drug Application for Starlix Tablets. As a follow-up to a July 31, 2000 telephone conversation with Nancy Sager, Environmental Assessment reviewer, Novartis is providing an amended page to the Environmental Assessment in the original NDA.

The amended page contains additional information on the microbial inhibition test in the Environmental Assessment section 6.5.1.

Should you have any comments or questions regarding this submission or any other Chemistry, Manufacturing and Controls issue please contact me directly at (973) 781-2735. If there are any general or clinical related issues please contact Carl Schlotfeldt, the DRA Therapeutic Area representative at (973) 781-3570.

Sincerely,

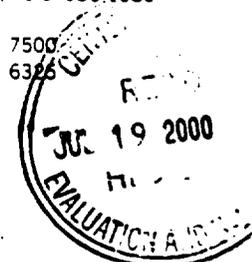
Sheryl LeRoy
Chemistry, Manufacturing and Controls
Drug Regulatory Affairs

 **NOVARTIS**

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~~CONFIDENTIAL~~

SM

July 17, 2000

John Jenkins, MD
Acting Director
Division of Metabolic and
Endocrine Drug Products/HFD-510
Office of Drug Evaluation II
Attn: Document Control Room 14B-19
Center for Drug Evaluation and Research
5600 Fishers Lane
Rockville, Maryland 20857

NDA No. 21-204
Starlix® (nateglinide) Tablets

Dear Dr. Jenkins:

We refer to our pending NDA 21-204 for Starlix (nateglinide). Attached is a replacement copy (electronic) of the Excel Spreadsheet for protocol B351. This is a replacement copy of the file that was provided initially via NDA amendment dated March 31, 2000.

As I mentioned in my phone message to Dr. Koller on Friday July 14, 2000, we detected a problem in the data for the derived variable NAIVE. A few patients were incorrectly categorized with respect to prior treatment for diabetes. This is the only variable in the file that is affected. The attached data set has been corrected. This problem does not affect the data in the final report for protocol B351 in the NDA.

The electronic file we are submitting has been rechecked for accuracy. In addition, it was scanned and found to be free of computer viruses using a program called VirusScan version 4.0.3a by Network Associates Inc.

If you have any questions about this submission please call me at (973) 781-3570.

Sincerely,

Carl Schlotfeldt
Associate Director
Drug Regulatory Affairs

/kp
Attachment
Submitted in duplicate
Desk Copy: Dr. E. Koller, HFD-510

REVIEWS COMPLETED	
CSC APPROVAL	
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CSC INITIALS	DATE



Novartis Pharmaceuticals Corporation
Drug Regulatory Affairs
59 Route 10
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July 14, 2000

John Jenkins, MD
Acting Director
Division of Metabolic and
Endocrine Drug Products/HFD-510
Office of Drug Evaluation II
Attn: Document Control Room 14B-19
Center for Drug Evaluation and Research
5600 Fishers Lane
Rockville, Maryland 20857

NDA No. 21-204
Starlix[®] (nateglinide) Tablets

Amendment - Statistical Section

Dear Dr. Jenkins:

We refer to our pending NDA 21-204 for Starlix (nateglinide). Attached are replacement copies (electronic) of the SAS data files for protocols B302 and B351 on CD ROM. This is in follow-up to our NDA amendments dated June 21, 2000 and July 6, 2000 which contained datasets for these two protocols.

The program that was used to generate data for the field NAIVE in the previous datasets (for these two protocols only) resulted in several patients being miscategorized with respect to prior treatment. That is the only variable affected. The information and data in the final reports for these two trials is unaffected.

The previously submitted Proc. Contents files for protocols B351 and B302 are correct.

The electronic files we are submitting have been rechecked for accuracy. In addition, these files were scanned and found to be free of computer viruses using a program called VirusScan version 4.03 by Network Associates Inc.

If you have any questions or comments on the above information, please call me at (973) 781-3570.

Sincerely,

Carl Schlotfeldt
Associate Director
Drug Regulatory Affairs

/kp

Attachments

Submitted in duplicate

Desk Copy: Ms. J. Mele, Statistician, c/o HFD-510

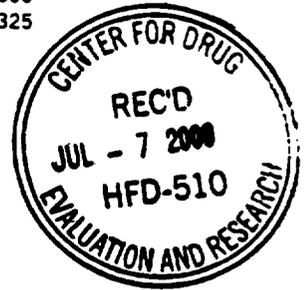
Information Copy (letter only): Ms. J. Weber, HFD-510

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NOVARTIS

ORIG AMENDMENT
BS

Novartis Pharmaceuticals Corporation
Drug Regulatory Affairs
59 Route 10
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Tel 973 781 7500
Fax 973 781 6325



July 6, 2000

John Jenkins, MD
Acting Director
Division of Metabolic and
Endocrine Drug Products/HFD-510
Office of Drug Evaluation II
Attn: Document Control Room 14B-19
Center for Drug Evaluation and Research
5600 Fishers Lane
Rockville, Maryland 20857

NDA No. 21-204
Starlix® (nateglinide) Tablets

Amendment – Statistical Section

Dear Dr. Jenkins:

We refer to our pending NDA 21-204 for Starlix (nateglinide). Attached are replacement copies (electronic) of the SAS data files for protocols B251, B252, B351 and B354 on CD ROM. This is in response to a request from the Statistical Reviewer (J. Mele) which was received via telefax dated June 19, 2000 (copy attached).

As further requested, the following information is provided in hard copy in conjunction with the SAS data sets for each of the three protocols.

- New Table 7.1 – 1a, Summary of Patient Disposition by Treatment Group and Visit (except for Study B354)
- New Table 7.1 – 2a, Summary of Discontinuations from Randomized Double-Blind Period by visit, reason and treatment group (except for Study B354)
- Explanation of Codes
- Proc. Contents

The electronic files we are submitting have been checked for accuracy. In addition, these files were scanned and found to be free of computer viruses using a program called VirusScan version 4.03 by Network Associates Inc.

If you have any questions or comments on the above information, please call me at (973) 781-3570.

Sincerely,

Carl Schlotfeldt
Associate Director
Drug Regulatory Affairs

REVIEWS COMPLETED	
CSO ACTION:	
<input type="checkbox"/> LETTER	<input type="checkbox"/> N.A.I. <input type="checkbox"/> MEMO
CSO INITIALS	DATE

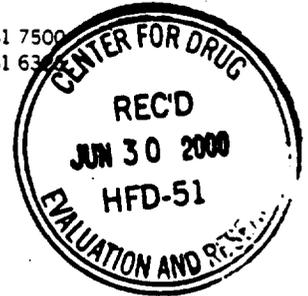
/kp
Attachments
Submitted in duplicate
Desk Copy: Ms. J. Mele, Statistician, c/o HFD-510
Information Copy (letter only): Ms. J. Weber, HFD-510

 **NOVARTIS**

BS

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Drug Regulatory Affairs
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John Jenkins, MD
Acting Director
Division of Metabolic and
Endocrine Drug Products/HFD-510
Office of Drug Evaluation II
Attn: Document Control Room 14B-19
Center for Drug Evaluation and Research
5600 Fishers Lane
Rockville, Maryland 20857

NDA No. 21-204
Starlix® (nateglinide) Tablets

Amendment – Statistical Section

Dear Dr. Jenkins:

We refer to our pending NDA 21-204 for Starlix (nateglinide). This is a follow-up to our previous amendment dated June 21, 2000.

Attached are replacement copies (electronic) of the SAS data files for protocols B202, B302 and B304 on CD ROM. As requested by the Statistical Reviewer (J. Mele) via telephone on June 23, 2000, we have added the variable "Duration of Diabetes (years)." The SAS name for this additional variable is DURDIA. Also attached to this letter is the updated Proc. Contents file in hard copy.

As mentioned before, please note that for protocol B304, center #29, the lone center in New Zealand (country code 12), was grouped with the centers in Australia (country code 11) when pooling of centers within the country was considered.

The electronic files we are submitting have been checked for accuracy. In addition, these files were scanned and found to be free of computer viruses using a program called VirusScan version 4.03 by Network Associates, Inc.

If you have any questions or comments on the above information, please call me at (973) 781-3570.

Sincerely,

Provisional to Dr. Mele

Carl Schlotfeldt

Carl Schlotfeldt
Associate Director
Drug Regulatory Affairs

efg 7/17/00

/kp
Attachments
Submitted in duplicate
Desk Copy: Ms. J. Mele, Statistician, c/o HFD-510
Information Copy (letter only): Ms. J. Weber, HFD-510



June 21, 2000

John Jenkins, MD
Acting Director
Division of Metabolic and
Endocrine Drug Products/HFD-510
Office of Drug Evaluation II
Attn: Document Control Room 14B-19
Center for Drug Evaluation and Research
5600 Fishers Lane
Rockville, Maryland 20857

NDA No. 21-204
Starlix® (nateglinide) Tablets

Amendment – Statistical Section

Dear Dr. Jenkins:

We refer to our pending NDA 21-204 for Starlix (nateglinide). Attached are replacement copies (electronic) of the SAS data files for protocols B202, B302 and B304 on CD ROM. This is in response to a request from the Statistical Reviewer (J. Mele) which was received via telefax dated May 26, 2000 (copy attached).

As further requested, the following information is provided in hard copy in conjunction with the SAS data sets for each of the three protocols.

- New Table 7.1 – 1a, Summary of Patient Disposition by Treatment Group and Visit
- New Table 7.1 – 2a, Summary of Discontinuations from Randomized Double-Blind Period by visit, reason and treatment group
- Data Format Information
- Proc. Contents

Please note that for protocol B304, center #29, the lone center in New Zealand (country code 12) was grouped with the centers in Australia (country code 11) when pooling of centers within the country was considered.

The electronic files we are submitting have been checked for accuracy. In addition, these files were scanned and found to be free of computer viruses using a program called VirusScan version 4.03 by Network Associates Inc.

If you have any questions or comments on the above information, please call me at (973)781-3570.

Sincerely,

Carl Schlotfeldt
Associate Director
Drug Regulatory Affairs

/cs
Attachment
Submitted in duplicate
Desk Copy: Ms. J. Mele, Statistician c/o HFD-510
Info Copy (letter only): Ms. J. Weber, HFD-510



DUPLICATE

 NOVARTIS

NEW CORRESP
BS

Novartis Pharmaceuticals Corporation
Drug Regulatory Affairs
59 Route 10
East Hanover, NJ 07936-1080

Tel 973 781 7500
Fax 973 781 6325

June 9, 2000

John Jenkins, MD
Acting Director
Division of Metabolic and
Endocrine Drug Products/HFD-510
Office of Drug Evaluation II
Attn: Document Control Room 14B-19
Center for Drug Evaluation and Research
5600 Fishers Lane
Rockville, Maryland 20857

NDA No. 21-204
Starlix® (nateglinide) Tablets



Dear Dr. Jenkins:

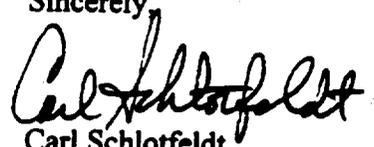
We refer to our pending NDA 21-204 for Starlix (nateglinide). Attached is a replacement copy of the SAS data files and summary tables on dropouts for protocol B202 on diskette. This is a partial follow-up to a telefax request as from the Statistical Reviewer (J. Mele) dated May 26, 2000.

Electronic Files in this submission:

- _____ - SAS files for B202
- _____ - Proc Contents B202
- _____ - Needed formats for B202
- _____ - Summary Tables of Dropouts

The electronic files we are submitting have been checked for accuracy. In addition, these files were scanned and found to be free of computer viruses using a program called VirusScan version 4.0.3a by Network Associates Inc.

If you have any questions or comments on the above information, please call me at (973) 781-3570.

Sincerely,

Carl Schlotfeldt
Associate Director
Drug Regulatory Affairs

/kp
Attachment (3.5" diskette)
Submitted in duplicate

Desk Copy: Ms. J. Mele, Biostatistician, c/o HFD-510

 NOVARTIS

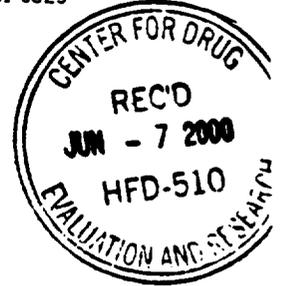
DUPLICATE

15P
COPY 2

Novartis Pharmaceuticals Corporation
Drug Regulatory Affairs
59 Route 10
East Hanover, NJ 07936-1080

Tel 973 781 7500
Fax 973 781 6325

June 5, 2000



John Jenkins, MD
Acting Director
Division of Metabolic and
Endocrine Drug Products/HFD-510
Office of Drug Evaluation II
Attn: Document Control Room 14B-19
Center for Drug Evaluation and Research
5600 Fishers Lane
Rockville, Maryland 20857

NDA No. 21-204
Starlix® (nateglinide) Tablets

Response to FDA Request
for Information

Dear Dr. Jenkins:

We refer to our pending NDA 21-204 for Starlix (nateglinide). Dr. Herman Rhee, Pharmacologist in HFD-510 contacted me by telephone on June 1, 2000 to request additional information regarding the doses used in the carcinogenicity studies in rats. The information is needed for the CAC.

The requested information is contained in the attached 3 page report entitled:

Calculations of safety factors and human equivalent doses derived
from rat carcinogenicity studies, dated June 1, 2000.

A copy was provided to Dr. Rhee via telefax on June 2, 2000.

Please contact me at (973) 781-3570 if you have any questions regarding this application..

Sincerely,


Carl Schlötfeldt
Associate Director
Drug Regulatory Affairs

CS/kp
Attachment
Submitted in duplicate
Desk copy: Ms. Jena Weber, HFD-510

ORIG AMENDMENT
BS

 NOVARTIS

Novartis Pharmaceuticals Corporation
Drug Regulatory Affairs
59 Route 10
East Hanover, NJ 07936-1080

Tel 973 781 7500
Fax 973 781 6325

ORIGINAL

June 1, 2000



John Jenkins, MD
Acting Director
Division of Metabolic and
Endocrine Drug Products/HFD-510
Office of Drug Evaluation II
Attn: Document Control Room 14B-19
Center for Drug Evaluation and Research
5600 Fishers Lane
Rockville, Maryland 20857

NDA No. 21-204
Starlix® (nateglinide) Tablets

Response to FDA Request
for Information

Dear Dr. Jenkins:

We refer to our pending NDA 21-204 for Starlix (nateglinide) and to the telefax from HFD-510 dated April 11, 2000. It contained the following request from the statistical reviewer:

For studies B202, B302, B304, B351, B356, B251, B252, B354
and B355, please provide copies of the final protocols with all
amendments incorporated.

Attached are copies of the protocols with all amendments incorporated for studies B251, B252, B351
and B356. In our previous amendment dated May 12, 2000 we submitted protocols with amendments
incorporated for B202, B302, B304 and B354. Per a recent teleconference with the Statistical
Reviewer (J. Mele) we understand that the protocol for B355 with amendments incorporated is not
needed at this time.

In the protocols for B251 and B252, some information from the amendments had to be incorporated
manually via "pen and ink." For all others the information was merged electronically.

If you have any questions regarding this submission, please call me at (973) 781-3570.

Sincerely,

Carl Schlotfeldt
Associate Director
Drug Regulatory Affairs

CS/kp
Attachments
Submitted in duplicate

Desk copy: Joy Mele, Biostatistician, c/o HFD-510
Information copy (letter only): Ms. Jena Weber, HFD-510

REVIEWS COMPLETED
CSO ACTION:
<input type="checkbox"/> LETTER <input type="checkbox"/> MAIL <input type="checkbox"/> FAX
CSO INITIALS



Novartis Pharmaceuticals Corporation
Drug Regulatory Affairs
59 Route 10
East Hanover, NJ 07936-1080

Tel: 973 781 7500
Fax: 973 781 6325

May 12, 2000

John Jenkins, MD
Acting Director
Division of Metabolic and
Endocrine Drug Products/HFD-510
Office of Drug Evaluation II
Attn: Document Control Room 14B-19
Center for Drug Evaluation and Research
5600 Fishers Lane
Rockville, Maryland 20857

NDA No. 21-204
Starlix® (nateglinide) Tablets

Response to FDA Request
for Information

Dear Dr. Jenkins:

We refer to our pending NDA 21-204 for Starlix (nateglinide) and to the telefax from HFD-510 dated April 11, 2000. It contained the following request from the statistical reviewer:

For studies B202, B302, B304, B351, B252, B354 and B355,
please provide copies of the final protocols with all
amendments incorporated.

Attached are copies of the protocols with all amendments incorporated for studies B202, B302, B304 and B354. This is a partial response. The remaining protocols will be submitted via a follow-up letter.

If you have any questions regarding this submission, please call me at (973) 781-3570.

Sincerely,

Carl Schlotfeldt
Associate Director
Drug Regulatory Affairs

CS/kp
Attachments
Submitted in duplicate

Desk copy: Dr. Joy Mele, HFD-715
Information copy (letter only): Ms. Jena Weber, HFD-510



Novartis Pharmaceuticals Corporation
Drug Regulatory Affairs
59 Route 10
East Hanover, NJ 07936-1080

Tel 973 781 7500
Fax 973 781 6325

May 4, 2000

John Jenkins, MD
Acting Director
Division of Metabolic and
Endocrine Drug Products/HFD-510
Office of Drug Evaluation II
Attn: Document Control Room 14B-19
Center for Drug Evaluation and Research
5600 Fishers Lane
Rockville, Maryland 20857

NDA No. 21-204
Starlix® (nateglinide) Tablets

Response to FDA Request
for Information

Dear Dr. Jenkins:

We refer to our NDA 21-204 for Starlix (nateglinide). We also refer to a recent request from Dr. H. Rhee, Pharmacology Reviewer (Preclinical) for certain data from the carcinogenicity studies and dose finding studies in electronic form. Attached is a CD-ROM containing the data requested. It consists of the following data files and readme files:

1. Tumor data (SAS Transport files)
 - Study 96001 (_____)
 - Study 942147 (_____)
 - Study 940143 (_____)
2. Data in Support of MTD (see readme file DJN FDA readme.doc)
 - A. Plots of Mortality Curves (SAS 6.12):
 - Study 96001 (filenames 96001_ _____)
 - Study 942147 (filenames AJO078_ _____)
 - Study 940143 (filenames YOC036_ _____)
 - B. Mortality Table (in non-cumulative form) for study 940136 (filename YOC036_ _____)
 - C. Analysis of Body weight in Study No. 940143 (filename YOC036_ _____)
 - D. Analysis of Body weights in Study No. 910923 (filename YOC_034_ _____)

Please contact me at (973) 781-3570 if you have any questions regarding these files. These files have been scanned for virus using Viruscan 4.0.3a.

Sincerely,

Carl Schlotfeldt
Associate Director
Drug Regulatory Affairs

CS/kp
Attachment (CD-ROM)
Submitted in duplicate
Desk copies: Dr. H. Rhee, HFD-510 (with CD-ROM)
Dr. K. Lin, HFD-715 (with CD-ROM)
Ms. J. Weber, HFD-510



Novartis Pharmaceuticals Corporation
Drug Regulatory Affairs
59 Route 10
East Hanover, NJ 07936-1080

Tel 973 781 7500
Fax 973 781 6325

April 20, 2000

John Jenkins, MD
Acting Director
Division of Metabolic and
Endocrine Drug Products/HFD-510
Office of Drug Evaluation II
Attn: Document Control Room 14B-19
Center for Drug Evaluation and Research
5600 Fishers Lane
Rockville, Maryland 20857

NDA No. 21-204
Starlix® (nateglinide) Tablets

Dear Dr. Jenkins:

We refer to our pending NDA 21-204 for Starlix (nateglinide). Attached is a replacement copy of the spreadsheet of glycemic data from protocol B355 on diskette. This is a further follow-up to an HFD-510 request as explained in our previous amendments to this NDA dated March 17, 24, and 31, 2000.

This completes our fulfillment of this request for replacement spreadsheets.

The electronic files we are submitting have been checked for accuracy against the SAS data from which these data were derived. In addition, these files were scanned and found to be free of computer viruses using a program called VirusScan version 4.0.3a by Network Associates Inc.

If you have any questions or comments on the above information, please call me at (973) 781-3570.

Sincerely,

Carl Schlotfeldt
Associate Director
Drug Regulatory Affairs

/kp
Attachment (3.5" diskette)
Submitted in duplicate

Desk Copy: Ms. J. Weber, HFD-510

Novartis Pharmaceuticals Corporation
Drug Regulatory Affairs
59 Route 10
East Hanover, NJ 07936-1080

Tel 973 781 7500
Fax 973 781 3590

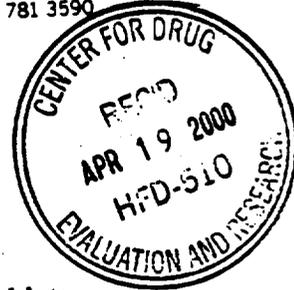
NOVARTIS

ORIGINAL

[Redacted]

SU

April 18, 2000



NDA No. 21-204
Starlix® (nateglinide) Tablets

120-DAY SAFETY UPDATE

John Jenkins, MD
Acting Director
Division of Metabolic and
Endocrine Drug Products/HFD-510
Office of Drug Evaluation II
Attn: Document Control Room 14B-19
Center for Drug Evaluation and Research
5600 Fishers Lane
Rockville, Maryland 20857

in
on

Dear Dr. Jenkins:

We refer to our pending NDA 21-204 for Starlix (nateglinide) submitted on December 17, 1999.

In accordance with 21 CFR 314.50(d)(5)(vi)(b), we are submitting the 4-month safety update report. This update follows the same format as that which we used to prepare the safety summary in the original NDA. The information in this update does not alter the safety conclusions contained in the original NDA.

As agreed during the pre-NDA meeting on January 19, 1999, this submission includes data tabulations in electronic form. Specifically, the SAS data sets from the two newly completed clinical trials included in this safety update, protocols B356E01 and 102, are provided as SAS transport files with associated data definition tables and annotated CREs. These files were prepared in accordance with the January 1999 FDA Guideline: "Providing Regulatory Submissions in Electronic Format - NDAs". The overall size of these files is and they are provided on one CD-ROM, which was created using software. The electronic files have been scanned with Network Associates VirusScan version 4.0.3A (formerly known as McAfee VirusScan).

Please contact me at (973) 781-3570 if you have any questions or comments on this submission.

Sincerely,

Carl Schlotfeldt

Carl Schlotfeldt
Associate Director
Drug Regulatory Affairs

REVIEWS COMPLETED
CSC ACTION:
<input type="checkbox"/> LETTER <input type="checkbox"/> N.A.I. <input type="checkbox"/> MEMO
CSC INITIALS
DATE

 **NOVARTIS**

DUPLICATE

Novartis Pharmaceuticals Corporation
Drug Regulatory Affairs
59 Route 10
East Hanover, NJ 07936-1080

Tel 973 781 7500
Fax 973 781 3590

BM

March 31, 2000



John Jenkins, MD
Acting Director
Division of Metabolic and
Endocrine Drug Products/HFD-510
Office of Drug Evaluation II
Attn: Document Control Room 14B-19
Center for Drug Evaluation and Research
5600 Fishers Lane
Rockville, Maryland 20857

NDA No. 21-204
Starlix® (nateglinide) Tablets

Dear Dr. Jenkins:

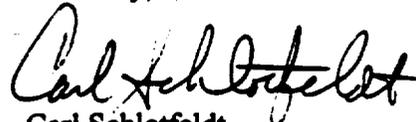
We refer to our pending NDA 21-204 for Starlix (nateglinide). Attached is a replacement copy of the spreadsheet of glycemic data from protocol B351 on diskette. This is a further follow-up to an HFD-510 request as explained in our previous amendments to this NDA dated March 17 and March 24, 2000.

We are in the process of preparing the replacement spreadsheet for protocol B355. It will be submitted shortly to complete our fulfillment of this request.

The electronic files we are submitting have been checked for accuracy against the SAS data from which these data were derived. In addition, these files were scanned and found to be free of computer viruses using a program called VirusScan version 4.0.3a by Network Associates Inc.

If you have any questions or comments on the above information, please call me at (973) 781-3570.

Sincerely, *n*



Carl Schlotfeldt
Associate Director
Drug Regulatory Affairs

/kp
Attachment (3.5" diskette)
Submitted in duplicate

Desk Copy: Ms. J. Weber, HFD-510



Novartis Pharmaceuticals Corporation
Drug Regulatory Affairs
59 Route 10
East Hanover, NJ 07936-1080

Tel 973 781 7500
Fax 973 781 3590

March 24, 2000

John Jenkins, MD
Acting Director
Division of Metabolic and
Endocrine Drug Products/HFD-510
Office of Drug Evaluation II
Attn: Document Control Room 14B-19
Center for Drug Evaluation and Research
5600 Fishers Lane
Rockville, Maryland 20857

NDA No. 21-204
Starlix® (nateglinide) Tablets

Dear Dr. Jenkins:

We refer to our pending NDA 21-204 for Starlix (nateglinide). Attached is a replacement copy of the spreadsheet of glycemic data from protocol B302.

At the pre-NDA meeting on January 19, 1999, Novartis Pharmaceuticals Corp. agreed to provide individual patient data (glycemic parameters only) for the major efficacy trials in this NDA in the form of Microsoft Excel spreadsheets. These files are included on the CD ROM (Review Aid) which accompanied the original NDA. Via telefaxes dated February 7 and 26, 2000 from the Project Manager in HFD-510, we were provided with instructions for modifying the content and format of the spreadsheets. Attached to this letter is the modified spreadsheet for protocol B302. It includes information from the trial in one spreadsheet as per instructions from HFD-510.

For the two remaining trials in this NDA for which spreadsheets were requested, (protocols B351 and B355) we are in the process of making the requested modifications.

The electronic files we are submitting have been checked for accuracy against the SAS data from which these data were derived. In addition, these files were scanned and found to be free of computer viruses using a program called VirusScan version 4.0.3a by Network Associates Inc.

If you have any questions or comments on the above information, please call me at (973) 781-3570.

Sincerely,

Carl Schlotfeldt
Associate Director
Drug Regulatory Affairs

/kp
Attachment (3.5" diskette)
Submitted in duplicate

Desk Copy: Ms. J. Weber, HFD-510

 **NOVARTIS**

DUPLICATE
COPY 2
NEW CORRESP
NV
Novartis Pharmaceuticals Corporation
Drug Regulatory Affairs
59 Route 10
East Hanover, NJ 07936-1080
Tel 973 781 7500
Fax 973 781 3500



March 21, 2000

NDA No. 21-204
Starlix® (nateglinide) Tablets

John Jenkins, MD
Acting Director
Division of Metabolic and
Endocrine Drug Products/HFD-510
Office of Drug Evaluation II
Attn: Document Control Room 14B-19
Center for Drug Evaluation and Research
5600 Fishers Lane
Rockville, Maryland 20857

Dear Dr. Jenkins:

We refer to our pending NDA for Starlix (nateglinide). This letter addresses issues associated with our product tradename and our recent request for a 90-Day Conference.

Tradename/Nomenclature Review

Novartis Pharmaceuticals Corp. has already made considerable financial investments in anticipation of launching the product with the Starlix tradename. Over a year ago, during the IND stage, we sought feedback from the FDA nomenclature committee, and we were informed that the tradename was judged to be acceptable.

We now understand that FDA will make another evaluation of the tradename as part of the NDA review. In light of the fact that we will continue to make investments based on the Starlix tradename, we request feedback on the results of this evaluation as soon as possible because it is a critical issue in our preparations for product commercialization.

90-Day Conference

In our previous NDA amendment dated March 9, 2000, we requested a 90-Day Conference in accordance with the regulations (21 CFR 314.102). On March 14, 2000 we were informed via telephone that the conference would not be scheduled at this time because FDA's review of this application had not yet advanced sufficiently to make such a meeting of value. It is our understanding that a conference could be scheduled later when the review advances sufficiently. On that basis, we plan to submit a meeting request, making reference to the previous request, in a month or so.

If you have any questions or comments on the above information, please call me at (973) 781-3570.

Sincerely,

Carl Schlotfeldt
Associate Director
Drug Regulatory Affairs

/kp
Submitted in duplicate
Desk Copy: J.Weber (HFD-510)



Novartis Pharmaceuticals Corporation
Drug Regulatory Affairs
59 Route 10
East Hanover, NJ 07936-1080

Tel 973 781 7500
Fax 973 781 3590

March 17, 2000

John Jenkins, MD
Acting Director
Division of Metabolic and
Endocrine Drug Products/HFD-510
Office of Drug Evaluation II
Attn: Document Control Room 14B-19
Center for Drug Evaluation and Research
5600 Fishers Lane
Rockville, Maryland 20857

NDA No. 21-204
Starlix[®] (nateglinide) Tablets

Dear Dr. Jenkins:

We refer to our pending NDA 21-204 for Starlix (nateglinide). Attached is a replacement copy of the spreadsheet of glycemic data from protocol B202.

At the pre-NDA meeting on January 19, 1999, Novartis Pharmaceuticals Corp. agreed to provide individual patient data (glycemic parameters only) for the major efficacy trials in this NDA in the form of Microsoft Excel spreadsheets. These files are included on the CD ROM (Review Aid) which accompanied the original NDA. Via telefaxes dated February 7 and 26, 2000 from the Project Manager in HFD-510, we were provided with instructions for modifying the content and format of the spreadsheets. Attached to this letter is the modified spreadsheet for protocol B202. It includes information from the Core and Extension phases of this trial in one spreadsheet as per instructions from HFD-510.

For the remaining trials in this NDA for which spreadsheets were requested, (protocols B302, B351 and B355) we are in the process of making the requested modifications.

The electronic files we are submitting have been checked for accuracy against the SAS data from which these data were derived. In addition, these files were scanned and found to be free of computer viruses using a program called VirusScan version 4.0.3a by Network Associates Inc.

If you have any questions or comments on the above information, please call me at (973) 781-3570.

Sincerely,

Carl Schlotfeldt
Associate Director
Drug Regulatory Affairs

/kp
Attachment (3.5" diskette)
Submitted in duplicate

Desk Copy: Ms. J. Weber, HFD-510

NOVARTIS

DUPLICATE
NEW DOCUMENT COPY 2

Novartis Pharmaceuticals Corporation
Drug Regulatory Affairs
59 Route 10
East Hanover, NJ 07936-1080

Tel 973 781 7500
Fax 973 781 3590

March 9, 2000



John Jenkins, MD
Acting Director
Division of Metabolic and Endocrine
Drug Products (HFD-510)
Office of Drug Evaluation II
Attn: Document Control Room 14B-04
Center for Drug Evaluation and Research
5600 Fishers Lane
Rockville, MD 20852

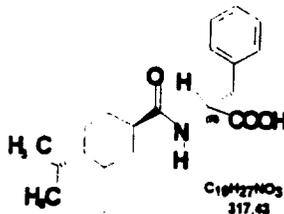
NDA No. 21-204
Starlix® (nateglinide) Tablets

Meeting Request

Dear Dr. Jenkins:

We refer to our pending NDA 21-204 for Starlix (nateglinide) oral tablets which was submitted on December 17, 1999 and is under review for the indication of Type 2 diabetes. In accordance with 21CFR314.102 we wish to schedule the 90-Day Conference with the Division. In accordance with the FDA guidance document entitled, "Formal Meetings With Sponsors and Applicants for PDUFA Products", background information to support this meeting request is provided as follows:

1. Product:
Starlix (nateglinide) NDA 21-204
2. Chemical Structure:



3. Proposed indication:
Type 2 diabetes mellitus
4. Type of meeting being requested:
Type C, NDA 90-Day Conference
5. Meeting Purpose:

We are requesting this meeting to discuss the general process by which we can support the Agency's review of the application, such that we would proceed directly to approval by the Primary User Fee goal date. We are also asking you to provide insight into the current status of your review, and to identify any potential issues which may have arisen thus far. While we acknowledge the relatively early stage of your review, we are requesting preliminary perspectives on some of the concepts in our draft labeling which pertain to the key attributes of our drug. Such topics for discussion are referenced in our enclosed agenda.

6. Objectives:
To obtain responses to the topics referenced above in Item 5 such that review and approval activities can proceed as optimally as possible.

7. Preliminary proposed agenda:
See attached draft agenda.
8. Specific questions:
See item 5 and our agenda.
9. The following Novartis Pharmaceuticals Corp. representatives are expected to attend:
Dr. Thomas Koestler, Global Head of Regulatory Affairs
Dr. Mathias Hukkelhoven, US Head of Regulatory Affairs
Mr. Adrian Birch, Global Head DRA, CME TA
Mr. Carl Schlotfeldt, Manager DRA, CME TA
Dr. Marjorie Gatlin, Director Clinical Research
Dr. James McLeod, Director Clinical Pharmacology
10. List of Agency Staff requested to attend:
Dr. John Jenkins, Acting Division Director
Dr. Saul Malazowski, Team Leader Diabetes in HFD-510
Dr. Elizabeth Koller, Medical Review Officer in HFD-510
Dr. Steven Johnson, Clinical Pharmacology Reviewer HFD-510
Ms. Jena Weber, Project Manager HFD-510
11. Supporting documentation:
At this time we expect to solicit your perspectives regarding issues identified in this correspondence, and we do not plan to make presentations. If there are topics you would like us to present, please advise us at your earliest convenience and approximately two weeks prior to the meeting we will provide copies of our slides and an outline of our presentation.
12. Suggested dates:
We would like to schedule this meeting as soon as possible and at a mutually convenient time. Early afternoon is preferred for same-day travel purposes, but that should not be considered as rate limiting.

I am the contact person if you have any questions or comments regarding this meeting request, and I can be reached at (973) 781-3570.

Yours truly,



Carl Schlotfeldt
Associate Director
Drug Regulatory Affairs

Attachments
Submitted in duplicate

Novartis Pharmaceuticals Corporation
Drug Regulatory Affairs
59 Route 10
East Hanover, NJ 07936-1080

Tel 973 781 7500
Fax 973 781 6325



January 31, 2000

NDA 21-204
Starlix® (nateglinide) Tablets

NDA Amendment - Chemistry, Manufacturing and Controls

FDA Center for Drug Evaluation and Research
Office of Drug Evaluation II
Document Control Room 14B-19
5600 Fishers Lane
Rockville, Maryland 20857

Attention: John Jenkins, MD, Director
Division of Metabolic and Endocrine Drug Products/HFD-510

Dear Dr. Jenkins:

Please refer to our above-referenced New Drug Application for Starlix Tablets. As a follow-up to a January 24, 2000 telephone conversation with the FDA chemistry reviewer, Dr. Xavier Ysern, Novartis is providing a replacement page for volume 2, page 44 of the original NDA.

The referenced page contains information on the packaging configurations for each tablet strength, along with the appropriate NDC numbers. Several typographical errors were corrected in the trade packaging section and three new NDC numbers have been assigned for the sample packages. Specifically, the following changes were made:

1. The size of the bottle for the 60mg bottle of 100's was corrected from 175 cc to 90 cc
2. The size of the bottle for the 180mg bottle of 100's was corrected from 75 cc to 175 cc
3. Bottle sizes for the samples have been specified
4. NDC numbers have been assigned for all samples in all container sizes

Should you have any comments or questions regarding this submission or any other Chemistry, Manufacturing and Controls issue please contact me directly at (973) 781-2735. If there are any

Starlix Tablets, NDA 21-204
CMC amendment
January 31, 2000

Page 2

general or clinical related issues please contact Carl Schlotfeldt, DRA Therapeutic Area representative at (973) 781-3570.

Sincerely,

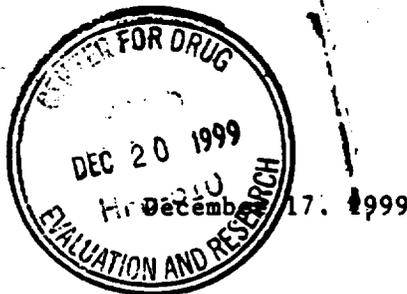


Sheryl LeRoy
Chemistry, Manufacturing and Controls
Drug Regulatory Affairs

Attachments
Submitted in Duplicate

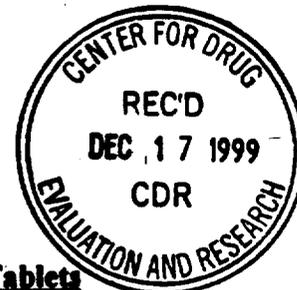
cc: Dr. Xavier Ysern (fax copy)

 **NOVARTIS**



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Food and Drug Administration
Center for Drug Evaluation and Research
Central Document Room
Park Building, Room 214
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Rockville, Maryland 20852

NDA No. 21-204
Starlix® (nateglinide) Tablets

ORIGINAL NEW DRUG APPLICATION

Dear Sir or Madam:

In accordance with 21 CFR 314.50, Novartis Pharmaceuticals Corporation herewith submits the original New Drug Application for Starlix (nateglinide) tablets for the treatment of Type 2 diabetes mellitus.

In the United States, Starlix was studied under IND _____ which resides in the Division of Metabolic and Endocrine Drug Products (HFD-510).

Starlix was evaluated in 12 controlled trials involving a total of 3,755 patients with Type 2 diabetes. Evidence from the pivotal controlled trials (Study Nos. B302, B351 and B354) as well as evidence from other controlled trials included in this application, demonstrate that Starlix improves glycemic control in patients with Type 2 diabetes, either alone or in combination with agents which have a complementary mode of action.

We believe that this NDA should be designated for priority review on the basis that Starlix provides a novel therapeutic approach, it is efficacious and answers an unmet need in the treatment of Type 2 diabetes, and it is very safe and well tolerated. We make this assessment in consideration of FDA's published criteria for priority review. This assessment is also consistent with our pre-NDA meeting discussion that affirmed the importance of the benefit to risk relationship in evaluating the priority of a therapy for Type 2 diabetes.

Starlix is novel because it is the first oral antidiabetic agent that _____ glucose by preferentially restoring early insulin secretion. The currently available therapies that increase insulin secretion do not preferentially stimulate early insulin secretion and are consequently associated with increased insulin exposure and its associated problems of late hypoglycemia and weight gain.

Through its novel mechanism of action, Starlix markedly reduces meal-related glucose excursions without inducing post-meal hyperinsulinemia. The long term result is significant improvement in overall control of glycemia in a large percentage of patients. This benefit is achieved with very low risk of hypoglycemia. In over _____ patient-years of exposure to Starlix to date, the overall incidence rate for confirmed hypoglycemia is extremely low (less than 3 %) and there have been no confirmed grade 3 or 4 events. Also, after thoroughly evaluating safety data for Starlix from all sources, we could not identify any other treatment-

related side effects such as GI disturbance, liver function or lipid abnormalities, or adverse cardiovascular or metabolic effects. Treatment-associated weight gain was modest - 1 kg or less. No clinically relevant interactions with commonly co-prescribed drugs were observed. To our knowledge, none of the previously approved drugs in this therapeutic class has shown such a favorable balance of benefits to risks. In addition, recently reported research findings in Type 2 diabetes suggest an important benefit of controlling glycemia. A strong correlation has been found between elevated glycemia and cardiovascular morbidity and mortality (see NDA Section 3, Pharmacological class, scientific rationale, intended use and potential clinical benefits).

As agreed during the pre-NDA meeting on January 19, 1999, this submission includes several NDA components in electronic form. All case report tabulations and case report forms (Sections 11 and 12 of this application) required under 21CFR314.50(f) are included in electronic form only via magnetic tape. These sections are organized as specified in the January 1999 FDA Guideline: "Providing Regulatory Submissions in Electronic Format - NDAs." For the key clinical studies in this submission [protocols B202, B202-E-01, B302, B304, B351, B351-E-01, B354, B355 and B356] data are provided as SAS transport files, along with associated data definition tables and annotated case report forms. For all other clinical studies, electronic data listings are provided as PDF files. The overall size of these electronic files is approximately [redacted]. The files are being submitted on a [redacted] tape (the format is [redacted] which holds [redacted] with compression). The tape was created with a Windows NT program called BackupExec.

Also, as specifically requested by Dr. Koller during the pre-NDA meeting, we are providing a patient listing of glyemic parameters (HbA_{1c}, FPG) and any reported events of symptoms suggestive of hypoglycemia for key trials. These data are displayed in an Excel spreadsheet on CD-ROM only.

In addition, to facilitate review, copies (non-archival) of the NDA summary, the integrated summaries, the narrative reports for the 9 key clinical studies, and the annotated proposed labeling are included electronically in Microsoft Word 97 on CD ROM. All the electronic files accompanying this submission have been scanned with Network Associates VirusScan Version 4.0.3A (formerly known as McAfee VirusScan).

A certified copy of Section 3 of this New Drug Application is being provided to our district office in compliance with the pre-approval inspection (PAI) requirements. Please note that the drug product will be manufactured in Switzerland and thus a foreign inspection, in addition to a local PAI, may be necessary.

We intend to _____

discussed more recently on October 29, 1999 via teleconference with the Medical Review Officer and Project Leader at HFD-510.

The FDA User Fee for this application (user fee ID 3853) was submitted on November 24 and December 3, 1999 (two payments).

Novartis Pharmaceuticals Corporation considers the information contained within this application to be confidential, and its contents are not to be disclosed without express written consent.

For questions or comments on this application, please contact the undersigned at (973) 781-3570.

Sincerely,



Carl Schlotfeldt
Associate Director
Drug Regulatory Affairs

Attachments: Form FDA 356H
Form FDA 3397
Volumes 1-312

Redacted

4

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