

CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

**APPLICATION NUMBER
21-204**

Administrative Documents

Time Sensitive Patent Information
pursuant to 21 C.F.R. 314.53
for
NDA 21-204

The following is provided in accordance with the Drug Price Competition and Patent Term Restoration Act of 1984:

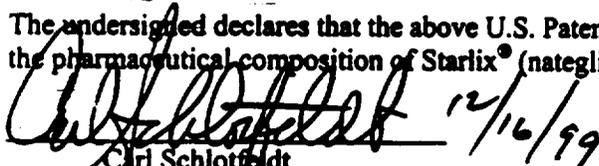
• Trade Name: Starlix
• Active Ingredient: Nateglinide
• Strengths: 60 mg., 120 mg. and 180 mg.
• Dosage Form: Tablets

A. U.S. Patent Number: Re. 34,878 (Reissue of U.S. Patent No. 4,816,484)
Expiration Date: March 28, 2006
Type of Patent: Compound per se and Pharmaceutical Composition
Assignee: Ajinomoto Co., Inc., Tokyo, Japan
U.S. Representative: Novartis Corporation
Patent & Trademark Dept. Bldg. A
564 Morris Avenue
Summit, NJ 07901-1027
USA

B. U.S. Patent Number: 5,463,116
Expiration Date: October 21, 2012
Type of Patent: Compound per se and Pharmaceutical Composition
Assignee: Ajinomoto Co., Inc., Tokyo, Japan
U.S. Representative: Novartis Corporation
Patent & Trademark Dept. Bldg. A
564 Morris Avenue
Summit, NJ 07901-1027
USA

C. U.S. Patent Number: 5,488,150
Expiration Date: January 30, 2013
Type of Patent: Compound per se and Pharmaceutical Composition
Assignee: Ajinomoto Co., Inc., Tokyo, Japan
U.S. Representative: Novartis Corporation
Patent & Trademark Dept. Bldg. A
564 Morris Avenue
Summit, NJ 07901-1027
USA

The undersigned declares that the above U.S. Patent Nos. 34,878, and 5,463,116 and 5,488,150 cover the pharmaceutical composition of Starlix® (nateglinide) as approved in NDA 21-204


Carl Schlotfeldt
Associate Director DRA

Exclusivity Checklist

NDA: 21-209			
Trade Name: STARLIX			
Generic Name: NABEGLIMIDE TABLETS, 60mg, 120mg, 180mg			
Applicant Name: NUVARIX			
Division: S10			
Project Manager: J. WEBER			
Approval Date:			
PART I: IS AN EXCLUSIVITY DETERMINATION NEEDED?			
1. An exclusivity determination will be made for all original applications, but only for certain supplements. Complete Parts II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following questions about the submission.			
a. Is it an original NDA?	Yes	<input checked="" type="checkbox"/> No	
b. Is it an effectiveness supplement?	Yes	<input type="checkbox"/> No	<input checked="" type="checkbox"/>
c. If yes, what type? (SE1, SE2, etc.)			
Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")			
		Yes	<input checked="" type="checkbox"/> No
If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.			
Explanation:			
If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:			
Explanation:			
d. Did the applicant request exclusivity?	Yes	<input type="checkbox"/> No	<input checked="" type="checkbox"/>
If the answer to (d) is "yes," how many years of exclusivity did the applicant request?			
IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS.			
2. Has a product with the same active ingredient(s), dosage form, strength, route of administration, and dosing schedule previously been approved by FDA for the same use?			
		Yes	<input type="checkbox"/> No <input checked="" type="checkbox"/>
If yes, NDA #			
Drug Name:			
IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS.			
3. Is this drug product or indication a DESI upgrade?			
		Yes	<input type="checkbox"/> No <input checked="" type="checkbox"/>
IF THE ANSWER TO QUESTION 3 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS (even if a study was required for the upgrade).			

PART II: FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES			
(Answer either #1 or #2, as appropriate)			
1. Single active ingredient product.	Yes	<input checked="" type="checkbox"/> No	
Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.	Yes	No	<input checked="" type="checkbox"/>
If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).			
Drug Product			
NDA #			
Drug Product			
NDA #			
Drug Product			
NDA #			
2. Combination product.	Yes	No	<input checked="" type="checkbox"/>
If the product contains more than one active moiety (as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)	Yes	No	<input checked="" type="checkbox"/>
If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).			
Drug Product			
NDA #			
Drug Product			
NDA #			
Drug Product			
NDA #			
IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS. IF "YES," GO TO PART III.			
PART III: THREE-YEAR EXCLUSIVITY FOR NDA'S AND SUPPLEMENTS			
To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2, was "yes."			
1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.	Yes	<input checked="" type="checkbox"/> No	
IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS.			

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

a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement? Yes No

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCKS.

Basis for conclusion:

b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application? Yes No

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

If yes, explain:

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

If yes, explain:

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

Investigation #1, Study # B 202, B 202, B, 304

Investigation #2, Study #: B 251, B 252

Investigation #3, Study #: B 351, B 359

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

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

Investigation #1 Yes No

Investigation #2 Yes No

Investigation #3 Yes No

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

Investigation #1 -- NDA Number

Investigation #2 -- NDA Number

Investigation #3 -- NDA Number

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

Investigation #1	Yes	No	<input checked="" type="checkbox"/>
Investigation #2	Yes	No	<input checked="" type="checkbox"/>
Investigation #3	Yes	No	<input checked="" type="checkbox"/>

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

Investigation #1 -- NDA Number	
Investigation #2 -- NDA Number	
Investigation #3 -- NDA Number	

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

Investigation #1	B 202, B 302, B 304
Investigation #2	B 251, B 252
Investigation #3	B 351, B 359

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

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

Investigation #1	B 02	Yes	No	<input checked="" type="checkbox"/>
IND#:				
Explain:				
Investigation #2	B 351	Yes	No	<input type="checkbox"/>
IND#:				
Explain:				
Investigation #3	B 314	Yes	No	<input type="checkbox"/>
IND#:				
Explain:				

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

Investigation #1	Yes	No	<input type="checkbox"/>
IND#:			
Explain:			
Investigation #2	Yes	No	<input type="checkbox"/>
IND#:			
Explain:			
Investigation #3	Yes	No	<input type="checkbox"/>
IND#:			
Explain:			

PEDIATRIC PAGE

(Complete for all original applications and all efficacy supplements)

NOTE: A new Pediatric Page must be completed at the time of each action even though one was prepared at the time of the last action.

V 21-204 Supplement # N/A Circle one: SE1 SE2 SE3 SE4 SE5 SE6

HFD-510 Trade and generic names/dosage form: Starlix (nateglinide) Tablets, 60 mg & 120 mg Action: AP

Applicant Novartis Therapeutic Class 1 S

Indication(s) previously approved N/A

Pediatric information in labeling of approved indication(s) is inadequate

Proposed indication in this application For the treatment of patients with Type 2 diabetes mellitus

FOR SUPPLEMENTS, ANSWER THE FOLLOWING QUESTIONS IN RELATION TO THE PROPOSED INDICATION.

IS THE DRUG NEEDED IN ANY PEDIATRIC AGE GROUPS? Yes (Continue with questions) X No (Sign and return the form)

WHAT PEDIATRIC AGE GROUPS IS THE DRUG NEEDED? (Check all that apply)

Neonates (Birth-1month) Infants (1month-2yrs) Children (2-12yrs) Adolescents(12-16yrs)

- 1. PEDIATRIC LABELING IS ADEQUATE FOR ALL PEDIATRIC AGE GROUPS.
2. PEDIATRIC LABELING IS ADEQUATE FOR CERTAIN AGE GROUPS.
3. PEDIATRIC STUDIES ARE NEEDED.
4. PEDIATRIC STUDIES ARE NOT NEEDED.
5. If none of the above apply, attach an explanation, as necessary.

ARE THERE ANY PEDIATRIC PHASE IV COMMITMENTS IN THE ACTION LETTER? Yes X No

ATTACH AN EXPLANATION FOR ANY OF THE FOREGOING ITEMS, AS NECESSARY.

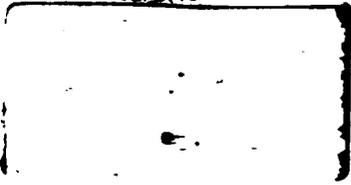
This page was completed based on information from Jena Weber, RHPM (e.g., medical review, medical officer, team leader).

JMWeber (6/15/00) e-copy on 12/27/00 Signature of Preparer and Title Date

Archival NDA 21-204 HFD-510/Div File NDA/PLA Action Package HFD-104/Peds/T.Crescenzi

(revised 3/6/00)

FOR QUESTIONS ON COMPLETING THIS FORM CONTACT, TERRIE CRESCENZI, HFD-104 (CRESCENZIT)



Starlix® (nateglinide) Tablets

NDA 21-204

**Novartis Pharmaceuticals Corp. Certification in compliance with the Generic Drug
Enforcement Act of 1992**

**Novartis Pharmaceuticals Corporation certifies that it did not and will not use in any capacity
the services of any person debarred under section 306(a) or 306(b) of the Federal Food, Drug
and Cosmetic Act in connection with this application.**

12/13/99

Date

**Carl Schlotfeldt
Associate Director
Drug Regulatory Affairs**

DISCLOSURE: FINANCIAL INTERESTS AND ARRANGEMENTS OF CLINICAL INVESTIGATORS

TO BE COMPLETED BY APPLICANT

The following information concerning see attached spreadsheets, who participated as a clinical investigator in the submitted study _____

see attached is submitted in accordance with 21 CFR part _____

54. The named individual has participated in financial arrangements or holds financial interests that are required to be disclosed as follows:

Please mark the applicable checkboxes.

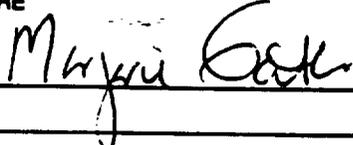
any financial arrangement entered into between the sponsor of the covered study and the clinical investigator involved in the conduct of the covered study, whereby the value of the compensation to the clinical investigator for conducting the study could be influenced by the outcome of the study;

any significant payments of other sorts made on or after February 2, 1999 from the sponsor of the covered study such as a grant to fund ongoing research, compensation in the form of equipment, retainer for ongoing consultation, or honoraria;

any proprietary interest in the product tested in the covered study held by the clinical investigator;

any significant equity interest as defined in 21 CFR 54.2(b), held by the clinical investigator in the sponsor of the covered study.

Details of the individual's disclosable financial arrangements and interests are attached, along with a description of steps taken to minimize the potential bias of clinical study results by any of the disclosed arrangements or interests.

NAME	TITLE
Marjorie Gatlin, MD	Executive Director CME Clinical Research
FIRM/ORGANIZATION	
Novartis Pharmaceuticals Corporation	
SIGNATURE	DATE
	14 Dec 99

Paperwork Reduction Act Statement

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number. Public reporting burden for this collection of information is estimated to average 4 hours per response, including time for reviewing instructions, searching existing data sources, gathering and maintaining the necessary data, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information to:

Department of Health and Human Services
Food and Drug Administration
5600 Fishers Lane, Room 14C-03
Rockville, MD 20857

Redacted 47

pages of trade

secret and/or

confidential

commercial

information

CERTIFICATION: FINANCIAL INTERESTS AND ARRANGEMENTS OF CLINICAL INVESTIGATORS

TO BE COMPLETED BY APPLICANT

With respect to all covered clinical studies (or specific clinical studies listed below (if appropriate)) submitted in support of this application, I certify to one of the statements below as appropriate. I understand that this certification is made in compliance with 21 CFR part 54 and that for the purposes of this statement, a clinical investigator includes the spouse and each dependent child of the investigator as defined in 21 CFR 54.2(d).

Please mark the applicable checkbox.

- (1) As the sponsor of the submitted studies, I certify that I have not entered into any financial arrangement with the listed clinical investigators (enter names of clinical investigators below or attach list of names to this form) whereby the value of compensation to the investigator could be affected by the outcome of the study as defined in 21 CFR 54.2(a). I also certify that each listed clinical investigator required to disclose to the sponsor whether the investigator had a proprietary interest in this product or a significant equity in the sponsor as defined in 21 CFR 54.2(b) did not disclose any such interests. I further certify that no listed investigator was the recipient of significant payments of other sorts as defined in 21 CFR 54.2(f).

Clinical Investigators	<input type="checkbox"/>	see attached
	<input type="checkbox"/>	spreadsheets
	<input type="checkbox"/>	

- (2) As the applicant who is submitting a study or studies sponsored by a firm or party other than the applicant, I certify that based on information obtained from the sponsor or from participating clinical investigators, the listed clinical investigators (attach list of names to this form) did not participate in any financial arrangement with the sponsor of a covered study whereby the value of compensation to the investigator for conducting the study could be affected by the outcome of the study (as defined in 21 CFR 54.2(a)); had no proprietary interest in this product or significant equity interest in the sponsor of the covered study (as defined in 21 CFR 54.2(b)); and was not the recipient of significant payments of other sorts (as defined in 21 CFR 54.2(f)).

- (3) As the applicant who is submitting a study or studies sponsored by a firm or party other than the applicant, I certify that I have acted with due diligence to obtain from the listed clinical investigators (attach list of names) or from the sponsor the information required under 54.4 and it was not possible to do so. The reason why this information could not be obtained is attached.

NAME	TITLE
Marjorie Gatlin, MD	Executive Director CME Clinical Research
FIRM/ORGANIZATION	
Novartis Pharmaceuticals Corporation	
SIGNATURE	DATE
	14 Dec 99

Paperwork Reduction Act Statement

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number. Public reporting burden for this collection of information is estimated to average 1 hour per response, including time for reviewing instructions, searching existing data sources, gathering and maintaining the necessary data, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information to the address to the right:

Department of Health and Human Services
Food and Drug Administration
5600 Fishers Lane, Room 14C-03
Rockville, MD 20857

MEMORANDUM

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

DATE: December 21, 2000

FROM: David G. Orloff, M.D. *D. Orloff 12-22-00*
Director, Division of Metabolic and Endocrine Drug Products

TO: NDA 21-204
Starlix (nateglinide) tablets
Novartis.

SUBJECT: Addendum to original memo dated December 7, 2000

Safety Updates

This addendum addresses pending items in the review of this NDA related to safety assessment and labeling. The original medical officer review by Dr. Koller addressed the safety information contained in the original NDA and examined deaths in the controlled trials, serious adverse events, discontinuations due to SAEs, notable AEs from post-marketing reports, hypoglycemia, weight gain, allergic reactions, and clinical laboratory abnormalities. Overall, nateglinide at the doses studied appeared to be extremely safe and well tolerated, with low rates of hypoglycemia attributed to the marginal efficacy of the drug in glucose lowering. Dr. Koller's review neglected the 4-month safety update submitted April 18, 2000, and a supplementary safety update at the end of the review cycle was not requested until early December. The latter was submitted on December 13, 2000 and consisted of an update of patient exposures, SAEs, and deaths. These updates have now been reviewed by Dr. Malozowski. His reviews are contained in the action package and raise no new safety issues.

The Integrated Summary of Safety submitted as part of the original NDA contained tabular summaries of the exposures by treatment group and duration in the completed clinical studies of Starlix monotherapy and combination therapy. The table below is reproduced from that submission. The majority of the Starlix exposure was at the 120 mg dose.

Duration (wks)	Starlix (n=1441)	Starlix: met (n=640)	Starlix: glyb (n=114)	Metformin (n=406)	Glyburide (n=293)	Placebo (n=458)
Any exposure	1440	640	114	406	293	458
≥ 12 weeks	1136	564	91	360	220	328
≥ 24 weeks	789	393	42	256	122	203
≥ 52 weeks	113	55	22	49	11	10

The 4-month safety update, submitted April 18, 2000, includes the safety information on an additional 464 Starlix-monotherapy-treated patients from 4 clinical pharmacology studies and NDA # 21-204
Drug: Starlix
Proposal: treatment of Type 2 DM
12/22/00

from 10 clinical trials, including one completed long-term extension study. This update covered the period from June 26, 1999, to January 31, 2000. The total safety exposure to Starlix monotherapy as of January 31, 2000 was reported as 1510. As of that cutoff date, an additional 363 patients were exposed to Starlix (the majority at 120 mg) for ≥ 12 weeks, 302 for ≥ 24 weeks, and 194 for ≥ 28 weeks.

The safety update submitted December 13, 2000, covering the period from February 1, 2000 to September 1, 2000, contains information on an additional 703 patients exposed to nateglinide in 3 completed and 12 ongoing studies, either as monotherapy or in combination with metformin. This includes an additional 173 patients exposed to the 180 mg dose either alone or in combination with metformin. Approximately half of these received drug for durations between 24 and 36 weeks or greater.

In both safety updates, the reporting rates for SAEs were similar between Starlix alone and placebo and less than reported among metformin-treated patients (alone or in combination with Starlix) or troglitazone-treated patients (alone or in combination with Starlix). The spectrum and frequency distribution of adverse events was likewise similar for Starlix and comparators, with the exception of a higher incidence of gastrointestinal adverse events with metformin and a slightly higher incidence of hypoglycemia with combination therapy with either metformin or troglitazone which reflects the risk of more intensive therapy aimed at control of blood glucose.

There were 3 deaths reported in the 4-month safety update, none apparently related to Starlix therapy but rather to the progression of underlying disease, and no additional deaths reported in the most recent update.

There were no clinical laboratory signals indicative of renal or hepatic impairment related to nateglinide therapy. The incidence of ALT or AST $> 200\%$ of baseline was $< 1\%$ for all nateglinide-treated patients and slightly less than placebo. One 59 year-old female experienced severe abdominal pain and headache beginning the day of the first dose of Starlix, accompanied by mild edema and "abnormal urine problems." Study drug was discontinued by the patient after 4 days, at which time SGOT, SGPT, and GGTP were all elevated. The patient had a complicated, multisystemic medical history and was on numerous concomitant medications. Laboratory abnormalities returned toward baseline over several weeks of follow up. The patient's presentation appears unlikely to be related to Starlix therapy.

A review of the deaths and serious adverse events reported in post-marketing in Japan does not clearly implicate drug in causality in reports of depression/suicide, cardiac arrhythmia, hepatic and biliary disease, musculoskeletal disease, hematologic abnormalities, or other organ system disorders.

Starlix in patients with renal insufficiency

Of note, one clinical study in patients with Type 2 diabetes and renal impairment (normal function vs. CrCl < 50 ml/min vs. CrCl 50-70 ml/min) was discussed in the 4-month safety update. A total of 34 patients were enrolled in this trial. After an 8-week run in on previous antidiabetic medication, patients were entered into an open-label 8-week treatment phase with Starlix 60 mg TID followed by forced titration to Starlix 120 mg TID. Once the results of the

NDA # 21-204

Drug: Starlix

Proposal: treatment of Type 2 DM

12/22/00

Phase 3 program became available and the sponsor recognized that patients previously chronically treated with other oral agents tended to deteriorate when switched to Starlix, this study was terminated. On page 14, the 4-month safety update contains the following statement: "As the patients in this trial became hyperglycemic on the 60 mg dose, this is especially contraindicated in patients with severe renal impairment due to advanced diabetes, the decision was made to terminate the trial."

Dr. Malozowski took note of this issue and recommended that the labeling be amended to address the use of the 60 mg dose in patients with renal insufficiency. The sponsor was asked to clarify this issue and responded on December 19, 2000, stating that "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." Data are presented showing the mean changes from baseline in HbA1C and FPG after 4 weeks of treatment and are consistent with other studies submitted showing deterioration in glycemic control in patients switched from chronic therapy with oral agents to Starlix. No changes to the labeling are necessary. The pharmacokinetic data support a recommendation that no dosage adjustment is necessary in patients with renal impairment.

Pending labeling issues

Finally, the sponsor has persisted in proposed labeling describing the results of the 24-week metformin combination therapy study that states the following:

Joy Mele has made the following comments in support of her recommendation against the inclusion of this statement: "The correlation between baseline and change is very low. The R^2 's are as follows: placebo (.06), Starlix 120 (.08), metformin 500 (.10), and the combination (.22). So, at most, for the combination, 22% of the variation in change in HbA1c from baseline can be explained by the baseline; for the Starlix 120 group only 8% of the variation can be explained by baseline. There is clearly a very weak relationship between baseline and response. The sponsor's statement is not supported by the data.

The sponsor has submitted rebuttals to these comments that we are unable to review in a timely fashion. The sponsor has been apprised of this and that the proposed labeling is not acceptable. The sponsor is free to resubmit this proposed labeling with supporting information for review at a later time.

Recommendation

Pending resolution of final labeling issues, this application may be approved.

MEMORANDUM

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

DATE: December 7, 2000

FROM: David G. Orloff, M.D. *D. Orloff 12-7-00*
Director, Division of Metabolic and Endocrine Drug Products

TO: NDA 21-204
Starlix (nateglinide) tablets
Novartis
Received December 17, 1999

SUBJECT: NDA review issues and action

Background

Nateglinide (Starlix) is an analogue of phenylalanine that binds with relatively low affinity (compared to repaglinide, glipizide, and glibenclamide) to the sulfonylurea (SFU) receptor and stimulates insulin release from pancreatic islet cells. It is rapidly absorbed and has a short duration of action. Based on these characteristics, it has been studied and will be recommended for use in Type 2 diabetes mellitus preceding each meal. This is with a goal of modulating prandial glucose excursions as part of an overall strategy to reduce glucose exposure in these patients.

The current application includes clinical studies that permit comparison of the efficacy and safety of Starlix as monotherapy versus placebo, glyburide, or metformin. In addition, combination studies with glyburide and metformin permit an assessment of the potential utility of such use compared to the individual drugs as monotherapies. A combination study with troglitazone was also conducted and reported, though this is no longer germane to the clinical use of nateglinide.

The application contains sufficient information to establish the safety and effectiveness of Starlix. Issues raised in review and discussed in more detail below include the following:

1. The sponsor has proposed administration of Starlix up to 30 minutes prior to meals with starting and maintenance doses of 120 mg three times daily. The Division recommends administration 1 to 10 minutes prior to each meal based upon the review by OCPB (Dr. Johnson).
2. The sponsor has proposed for marketing three doses (60, 120, and 180 mg). Overall, there is a poor dose-response seen with this agent. However, downward dose adjustment may be necessary in specific instances. In addition, subgroup analyses suggest that some individuals may derive additional glucose lowering benefit from higher doses (e.g., 180 mg).

NDA 21-204
Starlix (nateglinide)
Novartis
12/07/00

3. Nateglinide is more effective than placebo as monotherapy. In patients previously treated with glyburide (and presumably other SFUs), switching to Starlix results in deterioration in glycemic control, suggesting that switching patients from SFU to Starlix is inadvisable. Starlix in combination with glyburide and presumably other SFUs provides no additive effect on glycemic control. Starlix in combination with metformin does have additive efficacy in the control of blood glucose.
4. In the clinical trials conducted for this NDA, Starlix showed very little potential to cause hypoglycemia.

Medical/Biometrics

The clinical portion of this NDA contains reports of 2 placebo-controlled dose-ranging studies; 2 fixed-dose, active-controlled trials, and 4 combination studies (3 metformin, 1 glyburide). A study of Starlix in combination with troglitazone was conducted but the results are moot in light of the removal of Rezulin from the market in early 1999. The principal studies supporting labeling were 8 to 24 weeks in duration. The sponsor's safety pool includes 3156 patients enrolled in 11 clinical studies. Among these, 798 patients were exposed to Starlix alone for ≥ 24 weeks, and 393 patients were exposed to Starlix plus metformin for ≥ 24 weeks. 113 Starlix-only and 55 Starlix plus metformin patients were treated for ≥ 52 weeks.

The design and results of these studies will be briefly summarized. Sources are the MOR by Dr. Koller, the Biometrics review by Dr. Mele, and the sponsor's integrated summaries.

Monotherapy in drug-naïve patients

Studies 202 (12 weeks) and 302 (24 weeks) enrolled diabetics not adequately controlled on diet therapy alone, entered them into a 4-week placebo and diet run-in, then randomized them to placebo or nateglinide 30 (202 only), 60, 120, or 180 mg TID with meals for 12 or 24 weeks, respectively.

Based on the primary endpoint of change from baseline in HbA_{1c} in the ITT group (LOCF), 30 mg was not significantly different than placebo, and this dose was dropped from further development. The mean absolute change from baseline across the other doses ranged, across the two studies, from -0.3 to -0.7% with a suggestion of a dose response. The mean absolute differences from placebo were only slightly greater as the placebo groups showed mean increases in HbA_{1c} or $< 0.2\%$.

The 180 mg TID dose was studied only in these two monotherapy trials (N~230). Dr. Mele's analyses and discussion of dose-response reveal two facts supporting the potential utility of the highest dose. First, there is a linear trend across the doses suggesting a greater response with higher dose, though it should be noted that she included placebo in these analyses. Nevertheless, it seems likely that the trend would persist even excluding placebo. She remarks that the greatest incremental increase in efficacy is seen with a doubling of the dose from 60 to 120 mg TID, suggesting perhaps that the sponsor should have studied 240 mg TID rather than 180 mg TID. Be that as it may, Dr. Mele's analyses of efficacy in clinically relevant subgroups of the study populations further suggests that older patients, heavier patients, and those with longer-standing diabetes may derive incremental benefit from 180 mg TID compared to 120 mg TID. As she suggests, this dose should be approved, assuming a satisfactory risk vs. benefit. From the trial

experience showing only rare instances of hypoglycemia (see Safety, below), there is no evidence of increased risk that would outweigh potential benefit of this higher dose in patients not adequately controlled on 120 mg TID either alone or in combination with metformin.

Another study, 355 (8 weeks), compared treatment with placebo, Starlix 120 TID, and glyburide 10 mg in patients previously on diet alone.

Monotherapy in patients previously on SFUs

Study 304 enrolled patients not adequately controlled on SFU, entered them into a 4-week glyburide 10 mg run-in, then randomized to continued glyburide 10 mg, nateglinide 60 or 120 mg TID before meals for 24 weeks.

For the ITT group (LOCF), the mean change in HbA1c from baseline to week 24 was positive in all three groups, though greater in the nateglinide treated groups (0.28% glyb, 1.3% N60, 1.1% N120). Dr. Mele's analysis of mean HbA1c by last week on study (page 18 of her review) shows that for those completing the 24 weeks, there was no mean change from baseline in the glyburide group and similar increases in the two nateglinide groups that were stable from 12 weeks onward.

The results of this study suggest that switching from SFU to nateglinide in patients not adequately controlled on the former will be of no benefit to patients, may result in deterioration of glycemic control, and therefore should not be recommended.

Studies of nateglinide in combination with glyburide or metformin

Study 251 enrolled patients not adequately controlled on SFU alone, entered them into an 8-week glyburide 10 mg run-in, then randomized them to glyburide 10mg alone, in combination with nateglinide 60, or in combination with nateglinide 120 mg for 12 weeks.

For the primary endpoint of change from baseline in HbA1c at week 12, there were no significant differences across the treatment groups. In short, there is no additive effect of combining nateglinide and glyburide 10 mg (and presumably other SFUs at maximal doses), as might be predicted from their shared molecular targets.

Study 351 enrolled patients not adequately controlled on diet alone, entered them into a 4-week diet run-in, randomized to placebo, nateglinide 120 TID, metformin 500 TID, or the combination for 24 weeks.

For the primary endpoint of change from baseline in HbA1c at week 24 in the ITT population (LOCF), combination therapy (-1.5% change) was significantly better than either individual therapy (N120 -0.5%, met -0.8%). In this study, there appeared to be no difference in glycemic control between the monotherapy arms, though testing for such a difference not an objective of the trial.

Study 354 enrolled patients not adequately controlled on metformin (≥ 1.5 g daily) alone, entered them into a 4-week run-in of metformin 2000 mg daily (1000 BID), randomized to

continued metformin 1000 BID, or metformin 1000 BID in combination with either nateglinide 60 or 120-mg TID for 24 weeks.

For the primary endpoint of change from baseline in HbA1c at 24 weeks, both combination therapy arms were statistically significantly different from metformin monotherapy. As expected, the metformin group showed only a minimal mean decrease in HbA1c (0.04%) while the two combination arms showed dose-dependent decreases of 0.4% and 0.7%, respectively.

Thus, metformin in combination with nateglinide produces additive effects on glycemic control.

Study 252 enrolled patients not adequately controlled on combination therapy with SFU and metformin (≥ 1.5 g daily), entered them into a 4 week run-in of SFU at the pre-study dose combined with metformin 500 mg TID, then randomized to metformin 500 TID, or the combination of metformin 500 TID with either nateglinide 60 or 120 mg TID for 12 weeks.

For the primary endpoint of change from baseline in HbA1c, it is notable that, across all three treatment groups, >90% of patients showed a deterioration in glycemic control. The addition of nateglinide appeared to attenuate this deterioration in a dose-dependent manner, with only the nateglinide 120 TID plus metformin group being significantly different from metformin alone. A completers analysis shows mean increases in HbA1c of ~2%, 1%, and 0.8% for the metformin, metformin plus nateglinide 60 TID, and metformin plus nateglinide 120 TID groups, respectively.

The results of this study demonstrate again that nateglinide does have an additive effect on glycemic control when given in combination with metformin. However, this study also serves to confirm other studies examining the efficacy of nateglinide 60 and 120 mg compared to SFU, demonstrating that, having switched patients from metformin plus SFU to metformin plus nateglinide, there is a consistent deterioration in glycemic control. Thus, at the doses proposed for marketing, nateglinide appears neither as effective as SFU as monotherapy, nor as effective as SFU as part of combination therapy with metformin.

Dr. Mele's Table 40 (page 50) summarizes data with regard to % response defined as a HbA1c less than 6.5% at endpoint in the combination therapy trials. This analysis very clearly confirms the primary endpoint findings in these studies, demonstrating the additive effect of nateglinide in combination with metformin as initial therapy or as add-on therapy in patients not adequately controlled on metformin alone.

The results with regard to change from baseline in fasting plasma glucose across the studies (secondary endpoint) were generally consistent with those relating the HbA1c.

Safety

As expected from the marginal efficacy of this drug, at the doses studied and proposed for marketing, the trials suggest a minimal risk of hypoglycemia. Across three studies (302, 355, and 351, total N=1550) up to 24 weeks in duration, there were 4 episodes of hypoglycemia in nateglinide-treated patients (N~950), one of them in a patient on combination metformin and

nateglinide 120 mg TID. There were 4 episodes in metformin-only-treated patients (N~170) and 1 episode associated with glyburide therapy (N~50).

Weight gain was seen in patients treated with nateglinide, either alone or in combination with metformin, as well as in glyburide-treated patients. Metformin, as expected, appeared to attenuate the weight gain seen with nateglinide. According to Dr. Mele's review, approximately half of the patients treated with nateglinide 120 or 180 mg gained 1 kg or more at week 24, and one-third gained 2 kg or more. There was a poor correlation between degree of weight gain and glycemic control.

There are no other notable safety issues arising from the trials.

Biopharmaceutics

After oral administration approximately 10 minutes prior to a meal, nateglinide is relatively rapidly absorbed, with T_{max} of < 1 hour. Absolute bioavailability is approximately 75%. Half-life is about 2 hours. Starlix is ~98% bound to plasma proteins. It is extensively metabolized by CYP 2C9 with three major metabolites, each possessing from 17-33% potency of parent compound. Nateglinide is an inhibitor of 2C9 but is neither a substrate of nor an inhibitor of CYP 3A4. Interaction studies with warfarin, however, showed no effect of nateglinide on warfarin kinetics or dynamics (PT). Nateglinide is predominantly cleared (~ 85%) by the kidney; the remainder is cleared in the feces.

The timing of administration of nateglinide in relation to a meal has significant effects on pharmacokinetics. Specifically, administration 1 to 10 minutes prior to the meal is associated with shorter T_{max} and higher C_{max} than if administered either fasting or 2 minutes after the meal. Likewise, the T_{max} for insulin was likewise delayed with administration of nateglinide in the fed state.

Protein binding of nateglinide was reduced in dialysis patients. Given the pre-existing propensity of these patients toward hypoglycemia, caution should therefore be exercised in the use of nateglinide in these patients. Diabetics with moderate or severe renal insufficiency showed a marked reduction in the clearance via the urine of parent drug (11% in normals, 3% in renal failure), though clearly the absolute difference was relatively small. In renal failure patients, whether on dialysis or not, T_{max} was slightly prolonged and C_{max} slightly reduced. AUC was not markedly affected. Mild hepatic impairment increased drug exposure, shortened T_{max} and half-life, and raised C_{max} after administration of nateglinide. Caution should be exercised in the use of nateglinide in diabetics with significant hepatic impairment.

These findings further emphasize the fact that monitoring of acute and chronic effects on glycemic control must be individualized, as for all diabetes treatments.

Pharmacology/Toxicology

Nateglinide showed little in the way of systemic toxicity beyond its pharmacodynamic action to stimulate insulin release and lower blood glucose. In repeat-dose studies in dogs treated with doses achieving exposures 130 times human therapeutic exposures, duodenal ulcers and small increases in ALT and bilirubin were observed. Nateglinide is neither mutagenic nor

NDA 21-204

Starlix (nateglinide)

Novartis

12/07/00

carcinogenic. In pups of female rabbits treated during pregnancy with doses associated with maternal and embryo toxicity and mortality, there was an increased incidence of gallbladder agenesis. This will be reflected in pregnancy labeling.

Chemistry

The chemistry, manufacturing, and controls information is satisfactory to judge the quality of the drug substance and the drug product, and the application can be approved from the standpoint of ONDC.

The establishment inspections were all acceptable.

The environmental assessment provided by the sponsor was reviewed and a finding of no significant impact was issued by ONDC.

DSI/Data Integrity/Financial disclosure

The Division of Scientific Investigations audited 4 study sites, 2 domestic and 2 foreign. Three inspections were largely unremarkable and no Forms 483 were issued. The 4th site, of _____ enrolled a total of 20 patients. The inspector inspected the records of 10 patients. The inspection did result in the issuance of a Form 483 citing failures to adhere to protocol, failures to maintain accurate records, and failures to assure continued IRB approval. In addition, subjects were enrolled who did not meet the entry criteria for weight and height, and the values for these parameters were altered accordingly in the records. In addition, data were collected outside of the timeframes specified in the protocol. A VAI-R letter was issued requesting the investigator to specify how he will avoid such deficiencies in future studies. DSI recommended that the Division consider whether the data from this site should be used.

Note that this site enrolled only 20 patients in study 302 (dose-ranging), which randomized a total of 697 patients across 64 centers in North America and Europe. It is highly unlikely that the exclusion of the data from this site would impact the final outcome of the study.

With regard to financial disclosure by clinical investigators, the sponsor submitted FDA forms 3454 and 3455 certified that no investigator received outcome payments, that no investigator disclosed a proprietary interest in the product or an equity interest in the company, and that no investigator was the recipient of significant payments of other sorts. The sponsor also provided an overview of the process used to collect information, which included an initial letter requesting financial disclosure information to all investigators and up to two follow up letters at progressive 4 week intervals as needed if no response was received. The sponsor further points out that methods used to minimize bias included independent data monitoring via Novartis or the contract research organization, multiple investigators in each study, and blinded, controlled study designs. The sponsor also provided spreadsheets showing sites, investigators, subinvestigators, for received, something to disclose (Y/N), details of the disclosure for 10 phase 3 trials and extensions.

Two investigators out of hundreds across the trials disclosed financial information.

A review of the spreadsheets was conducted. The findings for study 351 will be summarized. This study had 83 sites, across which a total of 6 principle investigators did not provide financial information. Among the ~350 subinvestigators, 49 (~15%) did not provide financial information. In several instances, there was no information from anyone affiliated with a given site. The two investigators with information to disclose, mentioned above, were involved in study.

A cursory review of the other financial disclosure information revealed that for the non-US studies, only principal investigators are listed. Throughout, there appears to be a high percentage of reporting, perhaps somewhat less for the non-US sites, but overall the pattern is similar to that seen in 351. The sponsor made a diligent effort to obtain the information and, for the most part, succeeded.

Overall, the financial disclosure information does not raise concerns over data integrity. The response rate was very high among principle investigators as well as among subinvestigators (~85-90%). There were only two among many hundreds of investigators and subinvestigators in the phase 3 trials who reported financial interest that might constitute a conflict of interest. It appears highly unlikely that exclusion of data from the few sites in which investigators did not provide financial information would significantly affect the outcomes of the studies submitted to the NDA.

OPDRA/nomenclature

The name "Starlix" was found to be acceptable.

Recommendation

This NDA should be approved. Nateglinide at doses of 60 mg, 120 mg, and 180 mg is clearly superior to placebo using change from baseline in HbA1c as the primary measure of efficacy. The sponsor's recommended starting and maintenance dose of 120 mg is acceptable. The 60 mg dose was also effective and safe and should be approved. The sponsor should be challenged to address the recommended use of this dose in labeling. The 180 mg dose does show some added efficacy beyond that provided by the 120 mg dose and should be approved to enable upward dose titration. The label should reflect this mode of use in the Dosage and Administration section.

Starlix should be indicated for the treatment of Type 2 DM either as initial therapy or as add-on therapy to metformin. There is no additive effect when nateglinide is combined with SFU. Furthermore, patients not adequately controlled on either SFU or metformin alone should not be switched to Starlix in light of an expectation of deterioration in glycemic control in a large percentage of patients.

The sponsor also proposed _____ in the label. The rationale is that nateglinide is a short-acting drug that stimulates insulin secretion from the pancreas, facilitated by increases in the ambient glucose concentration, and that, taken immediately prior to a meal, acts in the immediate post-prandial phase to reduce glucose excursions. Because of its intended mode of use, its short duration of action, this, then, is the contribution Starlix makes glycemic control, ultimately reflected in a decrease in HbA1c.

The Division has not previously accepted such data in labeling, insofar as _____ is not an accepted surrogate for overall glycemic control. Specifically, it ignores the between-meal glucose level and thus is a measure that fails to take into account a significant fraction of the daily glucose exposure. While _____ "control" may describe the pharmacodynamic mechanism of action of nateglinide as an antidiabetic agent, it adds little to an understanding of the expected benefit of the drug. This is assessed in clinical practice as in trials and thus in labeling by following HbA1c. I concur with the team's recommendation not to include the _____ data.

Dr. Malozowski has recommended a phase 4 commitment to conduct a multiple-dose PK study in patients with renal insufficiency to better characterize the behavior of the drug in these patients. In discussion with Dr. Johnson of OCPB, the short half-life of the drug (2-4 hours), even in patients with renal insufficiency, suggests that accumulation of drug after multiple dosing is not to be expected. Therefore, Dr. Johnson maintains that there is nothing that will be further learned from the multiple-dose PK study in these patients. I concur.

APPEARS THIS WAY
ON ORIGINAL



Memorandum

Date: 11/21/00

NOV 21

From: Saul Malozowski, MD, PhD

Medical Team Leader, Division of Metabolic and Endocrine Drug Products, HFD-510

Subject: NDA 21-104. Starlix, Nateglinide. Sponsor: Novartis

To: David Orloff, MD
Director, DMEDP, HFD-510

Starlix is a non-sulfonylurea insulin secretagogue that acts through the SFU receptor, inducing a rapid release of endogenous insulin. This NDA presents data on more than 3000 individuals. Approximately 2500 patients with type 2 diabetes were enrolled either in phase 2 or 3 studies. The randomized double blind phase 3 studies lasted up to 24 weeks.

Satrlx administration results in a rapid but limited insulin release. This speedy action provides the following advantages: a) it can be used just before meals, and b) induces a rapid and limited insulin release that occurs with the ingestion of the meal, reducing the chances for hypoglycemia, the most common serious adverse event for insulin secretagoges.

On the other hand, the data provided by the sponsor in the PK/PD studies suggest the following, a) there is a great variability in its absorption depending on the feeding status and the meal composition, b) the doses tested (30, 60, 120, and 180 mg) do not show a pharmacodynamic proportional effects: all doses induce *similar* glucose reductions questioning the value of offering different dosages strengths, c) the insulin peak induced by Starlix, due to its short duration and magnitude, may or may not suffice to normalize glucose.

Efficacy

The studies performed by the sponsor support the efficacy of this drug in subjects with type 2 diabetes because:

1. A consistent decrease in HbA1C was seen in all studies with Satrlx.
2. The differences in HbA1 levels with diverse direct comparators did not exceed 1 %.
3. The differences were statistically significant.
4. In the fixed dose studies, the mean change in the HbA1C responses ranged from -0.4 (60 mg dose) to -0.7 (120 and 180 mg doses).

Other important efficacy issues are as follows:

1. The 30-mg dose was shown not to be effective in one study and it was subsequently not used in further studies.

The 180-mg dose was not used in any of the combination/add-on studies but it was used in the fixed dose studies, which are comparator studies.

There is no difference in responses as evaluated by changes in HbA1C by gender or age. Patients on Glyburide having inadequate control when switched to Starlix showed deterioration in glucose control.

5. Although Starlix acutely resulted in glucose reduction than Glyburide at hour two, at four hours, this parameter was similar for both drugs.
6. Submaximal Metformin (1500 mg) is more effective than Starlix (-0.8% vs -0.5%, respectively). However, when looking at naïve patients alone, there was no difference between these 2 active groups ($p > .3$).
7. Starlix in combination with Metformin improves glycemic control.
8. We lack information on the use of Starlix with other compounds (insulin, glitazones, acarbose, etc.)
9. The length of the studies (≤ 24 weeks) limit our understanding of the sustainability of Starlix effects.
10. Starlix appears to be neutral in affecting lipid parameters. The changes observed in the studies are not clinically significant.
11. The 180 mg dose was studied in a single clinical trial. The statistical reviewer stated that "The distribution of HbA1c change from baseline for placebo and for each dose of Starlix; the lowest dose of 30 mg was not significantly different from placebo while each of the three higher doses (60, 120 and 180) were at $p < .0001$ Subgroup analyses revealed that patients older than 58 or with diabetes for more than 3 years or with BMI > 30 benefited from the 180 mg dose."
12. The differences in efficacy were more slightly higher with the higher Starlix doses, but the clinical significance of these differences are dubious.

The Sponsor proposes a starting dose of 120 mg. This underscores the potential lack of need for the 60 mg dose. In addition, only a small number of patients were treated with the 180 mg dose, limiting our ability to properly assess its efficacy and safety.

Safety

1. No serious adverse events were reported during the studies.
2. The doses of 60, 120 and 180 mg offer a similar safety profile. Again, only a small number of patients, however, were treated with the 180 mg dose.
3. The lack of serious reports of hypoglycemia, is a reflection of the benefits of Starlix's PD properties when taken with meals. It also signals the short and limited pharmacological activity as reflected by the changes seen in HbA1C.
4. Due to its mechanism of action (increase in insulin release) weight gain was seen with Starlix. No clear correlation was seen, however, between weight increase and improvements in glucose control.
5. In combination with metformin the weight increase was less marked.
6. This product is already marketed overseas. Adverse events have been reported, but the attribution to the drugs remains to be properly determined.
7. Single PK/PD studies suggest that Starlix is differentially cleared in subjects with renal insufficiency. In addition, a postmarketing report of hypoglycemia from Japan in a subject with renal insufficiency is strongly suggestive that patients with renal impairment may be more prone to hypoglycemia secondary to Starlix administration. Because renal insufficiency is a frequently associated to diabetes, clarification of Starlix PK/PD properties when chronically administered in patients with renal impairment would be highly desirable.

**STATISTICAL REVIEW AND EVALUATION
CLINICAL STUDIES**

NDA #: 21-204
Drug: Starlix (nateglinide) Tablets
Sponsor: Novartis Pharmaceuticals Corporation
Indication: Treatment of Type 2 diabetes mellitus
Date of Submission: 12/17/99
Statistical Reviewer: Joy Mele, M.S. (HFD-715)
Volume Numbers in Statistical Section: Volumes 1, 199-311
Medical Input: Elizabeth Koller, M.D. (HFD-510)

INTRODUCTION	2
REVIEWER'S METHODS.....	2
FIXED-DOSE STUDIES	3
STUDY B202 (CONDUCTED 1/96 TO 4/97)	5
STUDY B302 (CONDUCTED 3/97 TO 1/99)	10
STUDY B304 (CONDUCTED 2/98 TO 6/99)	15
SUBGROUP RESULTS FOR FIXED DOSES OF NATEGLINIDE.....	19
DOSE RESPONSE ASSESSMENT	24
LIPIDS.....	28
WEIGHT GAIN	29
REVIEWER'S COMMENTS ON FIXED DOSE STUDIES	30
COMBINATION STUDIES.....	31
STUDY B251 (CONDUCTED 2/96 TO 4/97)	32
STUDY B252 (CONDUCTED 10/96 TO 6/98)	36
STUDY B351 (CONDUCTED 8/97 TO 4/99)	40
STUDY B354 (CONDUCTED 11/97 TO 5/99)	45
REVIEWER'S COMMENTS ON COMBINATION STUDIES	49
EXTENSION STUDIES.....	51
REVIEWER'S COMMENTS ON LABELING	54
OVERALL CONCLUSIONS.....	56
APPENDIX 1.....	57
APPENDIX 2.....	58
APPENDIX 3.....	59

Keywords: Clinical Studies, add-on design, dose-response, Type 2 diabetes
Abbreviations: NAT=nateglinide TROG=troglitazone GLB=glibenclamide
 PLA=placebo MET=metformin GLY=glyburide

Introduction

The sponsor has presented the results of nine controlled clinical trials (Table 1) to establish the efficacy and safety of nateglinide (an amino acid derivative) for the treatment of Type 2 diabetes as monotherapy or add-on/combination¹ therapy. As a result of discussions with the medical reviewer (Dr. Koller), this reviewer did not review Studies B355 and B356. Study B355 was a short study of only 8 weeks with a primary endpoint of post-prandial glucose excursion; an endpoint not acceptable by the medical division as a primary endpoint for establishing efficacy for a drug to treat type 2 diabetes. Study B356 is a study designed to assess the efficacy of nateglinide plus troglitazone; troglitazone was removed from the market this year and therefore the medical division will not consider combination therapy with troglitazone.

Table 1. Double-Blind, Randomized, Parallel-group, Controlled Clinical Trials

Design	Study Numbers (Doses of nateglinide 3X per day)
Fixed Dose, Placebo-controlled	B202 (30, 60, 120 and 180 mg) B302 (60, 120 and 180 mg)
Fixed Dose, Active- controlled	B304 (60 and 120 mg)
Fixed Dose, Placebo and Active- controlled	B355 (120 mg)
Combination	B252 (60 and 120 mg + metformin) B351 (120 mg + metformin) B354 (60 and 120 mg + metformin) B251 (60 and 120 mg + glyburide) B356 (120 mg + troglitazone)

Four doses of nateglinide were studied; 30, 60, 120 and 180 mg given before each meal (three times a day). The sponsor's proposed label recommends a starting and maintenance dose of 120 mg and titration to 180 mg for non-responders. For add-on therapy, either 60 mg or 120 mg is recommended.

Reviewer's Methods

All tables and figures presented in this review were created by this reviewer.

Data was available via CDER's Electronic Document Room; however this data was not usable for a number of reasons (e.g. only last-observation-carried-forward (LOCF) data, missing important variables, not organized according to our guideline for SAS datasets, etc.). This reviewer requested additional SAS datasets and the sponsor complied readily.

A DSI report was received on one German center in Study B354 that noted problems with informed consent and IRB approval. DSI reviewed data on the subjects in this center and found it acceptable. This reviewer believes there is no reason to exclude this data from the analyses. Nevertheless, as suggested by the medical reviewer, this reviewer checked the impact of this center's results on the overall study results and found no evidence of biased results.

The primary efficacy variable in all studies was change from baseline at endpoint for HbA1c. For a few studies, fasting plasma glucose (FPG) was also named as a primary efficacy variable. This reviewer has presented the results for both variables for all studies. Subgroup

¹ In some of the trials nateglinide is added to an existing therapy while in others patients are switched from placebo to nateglinide plus another active therapy. The sponsor refers to all these trials as combination trials and this reviewer has done likewise.

results are only shown for HbA1c. Data were analyzed using an analysis of covariance model with baseline as the covariate and with treatment and country or center as factors. This reviewer chose to use country instead of center in the model when there were several countries with small centers of variable sizes while the sponsor chose to pool small centers and use center in their model. Regardless of which factor was used, the results were comparable.

In addition to the efficacy endpoints, this reviewer analyzed the lipid and weight data since changes were anticipated on these measures.

This reviewer performed subgroup analyses for data from the fixed dose studies. The sponsor only presented subgroup analyses for the 120 mg dose which is insufficient.

In all studies, the sponsor computed baseline as the average of Weeks -2 and 0 (the only exception is Study B252 where only Week 0 was measured). For naïve patients, the baseline is quite stable during the run-in while for previously treated patients withdrawn from treatment, baseline increases during run-in. Averaging for the previously treated group will tend to underestimate the magnitude of the effect since the baseline will be decreased by the averaging. For the placebo-controlled fixed dose studies, less than 25% of the patients were previously treated so the effect of averaging on the overall estimates is negligible.

Fixed-dose Studies

The sponsor presented the results of three clinical trials (Table 2) which were designed to examine the efficacy of 4 fixed doses of nateglinide (30, 60, 120 and 180 mg per meal). Two studies (B202 and B302) were placebo controlled and one (B304) was glyburide-controlled. Studies B302 and 304 were Phase III trials that were considered pivotal by the sponsor.

Table 2. Reviewer's Table of Double-Blind, Randomized, Parallel-group, Controlled Clinical Trials

Study Number	Design	NIDDM Patient Population	Treatment Arms (N)	Duration of Treatment
B202	Fixed dose placebo-control	Diet-treated	NAT 30 mg (51) NAT 60 mg (58) NAT 120 mg (63) NAT 180 mg (57) PLA (60)	12 weeks
B302	Fixed dose placebo-control	Diet-treated	NAT 60 mg (174) NAT 120 mg (172) NAT 180 mg (175) PLA (176)	24 weeks
B304	Fixed dose active-control	Previously treated with diet + sulfonylureas	NAT 60 mg (187) NAT 120 mg (187) GLB 10 mg (185)	24 weeks

Statistical methods for fixed dose studies

The intent-to-treat (ITT) population is defined as all randomized patients who have baseline data and at least one efficacy measure on treatment. For patients missing the final week on study, the last observation is carried forward (LOCF). Baseline is computed as the average of Weeks -2 and 0 as specified in the protocols.

According to the protocols of Studies B202, B302 and B304, an ANOVA or ANCOVA to compare each dose to placebo or glyburide was planned. The model was to include terms for treatment, center, strata or baseline and terms for interaction. For Study B202 the interaction terms would be discarded if non-significant at $\alpha < .10$. For the other 2 studies, the plan was to keep the interaction terms in the model. The analyses carried out by the sponsor included both the treatment by center and treatment by baseline (or strata) interactions in the model regardless of significance.

For all three studies, this reviewer used an ANCOVA model to analyze the data. This model included treatment and country as main effects and baseline (HbA1c or FPG) as the covariate. Tests for interactions were made and found to be non-significant. The relationship between baseline and response was examined graphically and with a correlation analysis; both suggested a relationship between the two measures however the correlation was relatively low with Pearson coefficients < .3, nevertheless the inclusion of the covariate in the model seems reasonable in spite of the low correlation due to the decrease in variance (r for the model is increased) and also due to the utility of the baseline-adjusted estimates particularly where baseline differences occur.

The inclusion of the interaction terms in the sponsor's models decreases the power to test the main effects and complicates interpretation of the estimates and is generally not recommended particularly when the interactions are not significant (as is the case here).

To assess dose response in Studies B202 and B302, the sponsor assessed linear and quadratic effects. This reviewer combined the results from both studies to characterize the dose response curve both graphically and through modeling.

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Study B202 (conducted 1/96 to 4/97)

Study B202 is a double-blind, multicenter, placebo controlled trial designed to assess three primary objectives; 1) nateglinide dose response relationship for HbA1c and FPG, 2) comparison of each nateglinide dose to placebo and 3) the safety of nateglinide. Following a single-blind screening period of 4 weeks (Weeks -4 to 0 (baseline)), patients were randomized to nateglinide 30, 60, 120 or 180 mg three times a day (10 minutes before each meal) or placebo and treated for 12 weeks. Randomization was stratified on HbA1c measured at Week -2 (6.8% to 8.0% versus >8.0% to 10.5%).

The primary efficacy endpoints in this study are change from baseline of HbA1c and FPG at Week 12. Baseline was computed as the average of Weeks -2 and 0.

Inclusion/Exclusion Criteria

Patients could enter the 4-week placebo run-in if they fulfilled the following criteria (this is a partial listing of all criteria):

1. Aged 30-75
2. History of NIDDM of at least 3 months
3. Diet therapy for at least one month prior to run-in
4. No history of chronic insulin therapy or therapy within 2 months with sulphonylureas, biguanides and α -glucosidase inhibitors.

Following the 4-week placebo run-in, patients were randomized to treatment if they fulfilled the following criteria (this is a partial listing of all criteria):

1. FPG \geq 7.8 mmol/l (140mg/dl) based on Week -4 and -2
2. No FPG > 15 mmol/l (>275 mg/dl) between Week -4 and Week -2
3. 6.8% \leq HbA1c \leq 10.5% based on Week -4 and -2

Patient Disposition

A total of 516 patients were screened at 31 centers in North America (6 centers) and Europe (25 centers); 289 patients were randomized to treatment (Table 3). About 92% of the patients completed the study; the highest retention rate was in the NAT 120 mg group (95%). Only one randomized patient was excluded from the ITT population due to a lack of post-baseline data.

Table 3. Study B202 Patient Disposition

	Placebo	NAT 30	NAT 60	NAT 120	NAT 180
Randomized	60 (100%)	51 (100%)	58 (100%)	63 (100%)	57 (100%)
Week 8	54 (90%)	47 (92%)	55 (95%)	62 (98%)	55 (97%)
Week 12	54 (90%)	44 (86%)	54 (93%)	60 (95%)	53 (93%)
ITT	60 (100%)	51 (100%)	58 (100%)	62 (98%)	57 (100%)

For placebo and the lowest dose (30 mg) of nateglinide, the major reason for dropout was withdrawal of consent (Table 4). For the highest dose (180 mg) of nateglinide, adverse events was the most common reason for dropout. For all reasons, the number of dropouts in each treatment group was very small (≤ 3 patients).

Table 4. Study B202 Reasons for discontinuation

	Placebo (n=60)	NAT 30 (n=51)	NAT 60 (n=58)	NAT 120 (n=63)	NAT 180 (n=57)
ADE	2 (3%)	0	1 (2%)	1 (2%)	3 (5%)
Protocol violation	1 (2%)	0	0	0	0
Consent withdrawn	3 (5%)	3 (6%)	1 (2%)	1 (2%)	1 (2%)
Death	0	1 (2%)	0	0	0
Other	0	3 (6%)	2 (3%)	1 (2%)	0

Patient Demographics

The treatment groups were comparable at baseline regarding baseline demographics (Table 5). The majority of the patients were male and Caucasian. Patients ranged in age from 31 to 75 years with a mean of about 57; about 25% of the patients were 65 years or older. More than 2/3 of patients were naive to drug treatment for diabetes.

Table 5. Study B202 Baseline demographics

	Placebo (n=60)	NAT 30 (n=51)	NAT 60 (n=58)	NAT 120 (n=63)	NAT 180 (n=57)
Age (years)					
Mean (SD)	57 (10)	58 (10)	56 (10)	54 (12)	57 (10)
Range	37-75	32-74	35-75	31-74	33-74
Race: Caucasian	97%	88%	93%	94%	91%
Gender: M/F	60%/40%	71%/29%	71%/29%	70%/30%	63%/37%
BMI					
Mean (SD)	28 (3)	29 (3)	28 (3)	29 (4)	29 (3)
Years of Diabetes					
Mean (SD)	5.4 (5)	4.5 (5)	6.2 (6)	4.4 (4)	3.7 (3)
Median	3.6	2.6	3.7	3.7	2.8
Range					
% Naive	65%	71%	72%	75%	75%
% Previously treated	35%	29%	28%	25%	25%

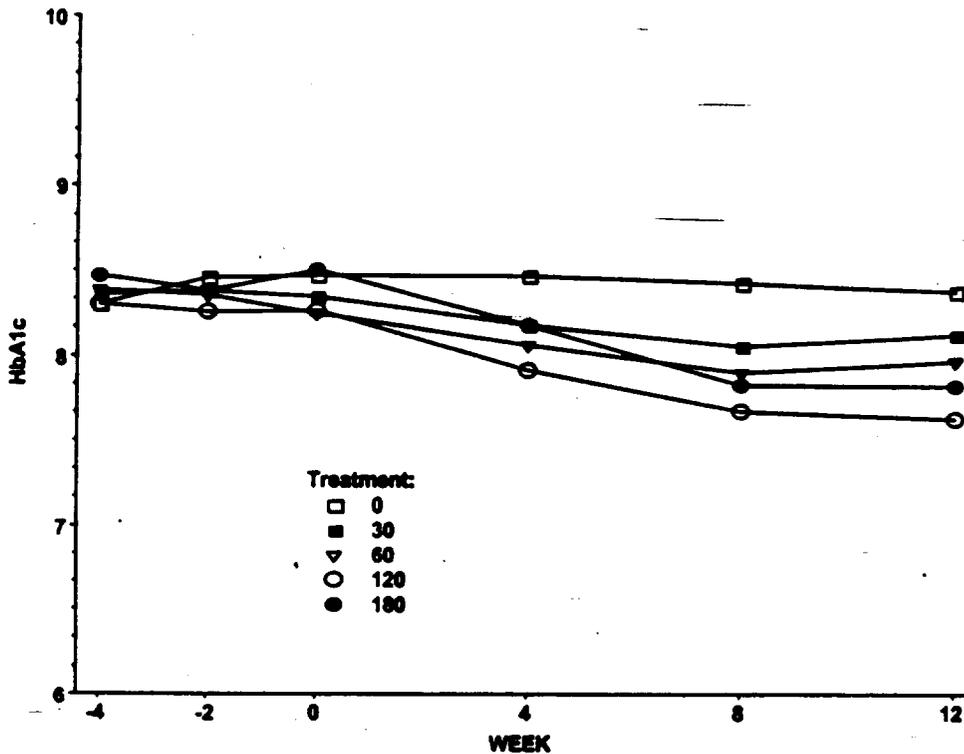
The most common medical conditions presenting at baseline were hypertension (38%), neuropathy (10%) and hypercholesterolaemia (10%).

Efficacy Results

HbA1c

HbA1c, a primary efficacy variable, was measured at Weeks -4, -2, 0, 4, 8 and 12. The mean results at each timepoint are depicted in Figure 1 below. Essentially no change in HbA1c is seen for the placebo group while all doses of nateglinide showed a decrease by Week 4 that was sustained for the 12 weeks of therapy.

Figure 1. Study B202 Mean HbA1c by week on study and by treatment group for observed cases.



The change from baseline at Week 12 for the ITT population (last-observation-carried-forward, LOCF) was the primary endpoint for assessing efficacy. The ITT results as well as the completer results at Week 12 are presented in Table 6 on the following page. As would be expected from the small number of dropouts, the estimates for completers are comparable to the LOCF estimates.

Recommendations:

Because the results of the studies indicate that this product is effective in patients with type 2 diabetes with a good safety profile, I recommend the drug to be approved. Numerous changes in the proposed label, however, need to be implemented to convey the results of the support studies in a more balanced manner. The dose to be marketed should be 120 mg because it was the most studied and the two other dose were either less efficacious (60 mg) or were no adequately studied (120 mg) for all proposed indications. Finally, I will also recommend a small phase 4 study to clarify the PK/PD properties of Satrix when given chronically in diabetic patients with renal insufficiency. It would be desirable to have the results of this study for evaluation before the end of 2001.

APPEARS THIS WAY
ON ORIGINAL

APPEARS THIS WAY
ON ORIGINAL

REQUEST FOR TRADEMARK REVIEW

To: Office of Postmarketing Drug Risk HFD-400
Attention: Jerry Phillips R.Ph., HFD-400, Parklawn Building, Room 15B23

From: Division of Metabolism and Endocrine D. P./ HFD-510
Attention: Dr. Xavier Ysem Phone: (301) 443-3510

Date: 27-JAN-2000

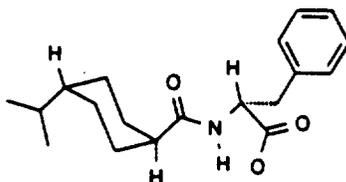
Subject: Request for Consultation. Assessment of a Trademark for a Proposed Drug Product

Proposed Trademarks: STARLIX

NDA #: 21-204

Drug Product Name Proprietary:
Nonproprietary/Established/USAN:

Starlix
Nateglinide



$C_{19}H_{27}NO_3$ MW = 317.43 *N*-(*trans*-4-Isopropyl cyclohexylcarbonyl)-D-phenylalanine

Other trademarks by the same firm for companion products: - N.A. -

Name and address of applicant: Novartis Pharmaceutical Corporation
59 Route 10
East Hanover, NJ 07936-1080

Indications for Use (may be a summary if proposed statement is lengthy): Treatment of Non-Insulin-Dependent Diabetes Mellitus

Dosage Form: Tablets Strength(s): 60-, 120- and 180-mg Route of Administration: Oral Dispensed: B

Initial comments from the submitter (concerns, observations, etc this year. The proprietary name Starlix™ was send for consultation on 21-JAN-1999 (clinical development of this product was in late stages and the sponsor planed to file NDA late 1999). The CDER Labeling and Nomenclature Committee found that name acceptable (consult 1152 dated 09-APR-1999).

filename: nda/21204tm.doc

Attached: Annotated Proposed Labeling
Draft Packaging label
Previous trademark consultation (consult # 1152, 21-Jan-1999 request/ 09-APR-1999 response)

CDER LABELING AND NOMENCLATURE COMMITTEE

CONSULT # 52 NFD# 50 PROPOSED PROPRIETARY NAME: _____ PROPOSED ESTABLISHED NAME: _____
ATTENTION: Kaver Ysem Starix natiprice

A. Look-alike/Sound-alike
Stimamx (NDA pending)

	Potential for confusion:
	Low <u>xxx</u> Medium _____ High _____
	Low _____ Medium _____ High _____
	Low _____ Medium _____ High _____
	Low _____ Medium _____ High _____
	Low _____ Medium _____ High _____

B. Misleading Aspects: _____

C. Other Concerns: _____

D. Established Name
 Satisfactory
 Unsatisfactory/Reason _____

Recommended Established Name _____

E. Proprietary Name Recommendations:
 ACCEPTABLE UNACCEPTABLE

F. Signature of Chair/Date: ISI 4/9/99

MEMORANDUM OF MEETING

Meeting Date: Friday February 11, 2000; @4:30pm, Room 1456

Application: Novartis, NDA 21-204 Starlix (nateglinide) Tablets

Type of Meeting: Filing meeting

Meeting Recorder and Chair: Jena Weber, RHPM 

FDA Attendees

Elizabeth Koller, M.D.	Medical Officer
Ron Steigerwalt, Ph.D.	Team Leader Pharmacology
Herman Rhee, Ph.D.	Pharmacologist
Xavier Ysern, Ph.D.	Chemist
Todd Sahlroot, Ph.D.	Team Leader Biometrics
Steven Johnson, Pharm.D.	Biopharm
Hae-Young Ahn, Ph.D.	Team Leader Biopharm
Jena Weber	RHPM

Meeting Objectives: To determine if this supplement is fileable, priority or standard review, advisory committee needed.

Comments:

Medical: Application is fileable, and should be designated as a **Standard** review (12 months). The sponsor is preparing data spread sheets for our review. Advisory committee could possibly be requested, but will not be initiated at this time. Inspection sites will be designated.

Pharmacology: Fileable, no unique issues.

Statistics: Filable; need EDR data for Studies B251 and B252. The company was notified and will provide data/information to Joy Mele, the biometrics reviewer for this NDA.

Chemistry: Fileable, chemistry appears adequate, stable compound.

Biopharm: Fileable, need electronic datasets.

Page 2

Conclusions:

1. Application is **fileable**.
2. Submission will be assigned **Standard review**, not priority.
3. No Advisory Committee will be requested at this time.
4. Need electronic datasets for BPH & STT reviewers, as well as electronic data and final reports from the rat and mouse carcinogenicity studies. Company will be notified.

ISI
2/15/00

Jena M. Weber.

CONSULTATION RESPONSE
Office of Post-Marketing Drug Risk Assessment (OPDRA)
(HFD-400)

DATE RECEIVED: 9/ 12/ 2000	DUE DATE: 11/ 10/ 2000	OPDRA CONSULT #: 00-0249
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TO:
David Orloff, M.D.
Director, Division of Metabolic and Endocrine Drug Products
(HFD-510)

THROUGH:
Jena Weber
Project Manager
(HFD-510)

PRODUCT NAME: Starlix (Nateglinide Tablets) DA #: 21-204	MANUFACTURER: Novartis Pharmaceuticals Corporation
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SAFETY EVALUATOR: Lauren Lee, Pharm.D.

OPDRA RECOMMENDATION:
OPDRA recommends the labeling revisions listed in this review. This is a follow-up review for OPDRA consult # 00-0040.

/S/ 11/7/00

Jerry Phillips, R.Ph.
Associate Director for Medication Error Prevention
Office of Post-Marketing Drug Risk Assessment
Phone: (301) 827-3242
Fax: (301) 480-8173

/S/ 11-7-00

Martin Himmel, MD
Deputy Director
Office of Post-Marketing Drug Risk Assessment
Center for Drug Evaluation and Research
Food and Drug Administration

Office of Post-Marketing Drug Risk Assessment
HFD-400; Rm. 15B-03
Center for Drug Evaluation and Research

PROPRIETARY NAME REVIEW

DATE REVIEWED: November 6, 2000
NDA#: 21-204
NAME OF DRUG: Starlix (Nateglinide Tablets)
NDA HOLDER: Novartis Pharmaceuticals Corporation

I. INTRODUCTION:

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.

.. 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.

III. RECOMMENDATION:

OPDRA recommends the above labeling revision that might lead to safer use of the product.

If you have further questions or need clarifications, please contact Sammie Beam at 301-827-3161

/S/

11/7/00

Lauren Lee, Pharm.D.
Safety Evaluator
Office of Post-Marketing Drug Risk Assessment

Concur: --

/S/

11/7/00

Jerry Phillips, RPh
Associate Director for Medication Error Prevention
Office of Post-Marketing Drug Risk Assessment

CC:

NDA: 21-204

Office Files

HFD-510; DivFiles; Jena Weber, Project Manager

HFD-510; David Orloff, Division Director

HFD-400; Jerry Phillips, Associate Director, OPDRA

Electronic only cc:

HFD-002: Heidi Jolson, Acting Deputy Center Director for Review Management

HFD-400: Peter Honig, Director, OPDRA

HFD-400: Sammie Beam, Project Manager, OPDRA

L:\OPDRA00\LEE\00-0249 STARLIX PART 2

T-CON

Note to NDA file 21-204

Novartis
Attention: Carl Schlotfeldt
Monday August 14, 2000

Phone: 973-781-3570

Topic: Review clock change from 10 to 12 months.

Participants:

Novartis

Carl Schlotfeldt
Adrian Birch

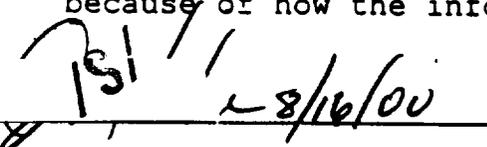
FDA

Elizabeth Koller, M.D.
Jena Weber, RHPM

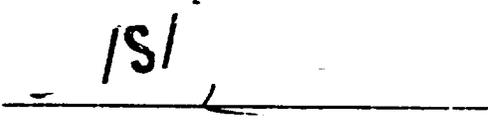
Novartis submitted NDA 21-204 for Starlix on December 17, 1999.

Synopsis of conversation:

Dr. Koller and I called Carl Schlotfeldt to inform him that due to the Division's heavy workload, the Starlix NDA will be reviewed under a 12-month clock (UEGD 12/17/00), instead of the 10-month clock (UEGD 10/17/00), that we ordinarily intended to use. In addition, we said that we would have to re-evaluate the spread sheet calculations because of how the information was set-up.



Jena Weber, RHPM



Beth Koller, M.D.

T-con

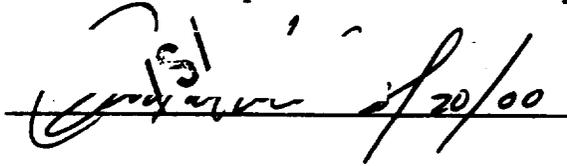
Note to NDA 21-204 (Starlix).

Novartis; conversation with Carl Schlotfeldt 973-781-3570.

Held on Thursday March 16th, 2000.

On March 9, 2000, we received a submission to the NDA from Novartis Regulatory Affairs person, Carl Schlotfeldt requesting a 90-day meeting with this Division. As this action is allowed under 21 CFR 314.102, and noting that the company had provided a purpose for this meeting complete with an agenda and objectives, I circulated this request to team members for comment before placing a meeting on the calendar. I told Mr. Schlotfeldt on March 10, 2000, that considering that the goal date for this application is not until October 17, 2000, and that none of the reviewers have started their evaluations, a meeting would not be useful.

After the reviewing team members and Dr. Jenkins concluded that this meeting would not serve a relevant purpose at this time, I phoned Mr. Schlotfeldt to inform him that we would NOT hold a meeting for the reasons mentioned above. He said that he would pass this along to his management and that they may propose another meeting in a month or six weeks. He added that the company wanted to keep the "lines of communication" open for discussion for any issues regarding their application.



A handwritten signature in black ink, appearing to read 'Jena Weber', with a horizontal line drawn underneath it. To the right of the signature, the date '3/20/00' is written.

Jena Weber, RHPM
HFD-510

APPEARS THIS WAY
ON ORIGINAL

T-CON

Note to NDA file 21-204

Novartis
Attention: Carl Schlotfeldt
Wednesday February 16, 2000 @ 8:30a

Fax: 973-781-3590

Topic: Priority Review for NDA

Participants:

Novartis

FDA

C. Schlotfeldt
A. Birch
M. Gatlin, M.D.
J. McLeod, M.D.
T. Koestler

— J. Jenkins, M.D.
S. Malozowski, M.D.
E. Koller, M.D.
— J. Weber, RHPM

Novartis submitted NDA 21-204 for Starlix on December 17, 1999. In their cover letter, they requested that priority review be granted on the basis that the drug is safe, well tolerated, and provides a novel therapeutic approach in the treatment of type 2 diabetes mellitus.

Synopsis of conversation:

- Drug appears to have good safety record and rapid onset of action.
- Novartis - drug safety and tolerability are the advantages with this product.
- FDA - preclinical data seem to indicate that Starlix does have some advantages, but not more than what is presently on the market. These are clinical practice arguments, and not regulatory claims.
- Agency feels that this application does not pose a significant advance over currently approved drug therapies, and will not be granted priority review; standard review clock will be used. Company may request a 90-day conference (as per 21 CFR 314.102) as appropriate.

JS 1/17/00

Jena Weber, RHPM

MEMORANDUM OF MEETING MINUTES

Meeting Date: Tuesday January 19, 1999

Time: 12 noon - 2pm

Location: Conf. Room "K"

Application: Reference IND (STARLIX)

Type of Meeting: Pre-NDA

Meeting Chair: Saul Malozowski, M.D.

Meeting Recorder: Jena Weber, CSO

FDA Attendees, titles, and Office/Division:

Saul Malozowski, M.D.	Team Leader, Medical Officer
Robert Misbin, M.D.	Medical Officer
Elizabeth Koller, M.D.	Medical Officer
Xavier Ysern, Ph.D.	Chemistry Reviewer
Jena Weber	RHPM

Novartis Attendees and titles:

Adrian Birch	DRA Director
Carl Schlotfeldt	DRA
Carole Smith, Ph.D.	Toxicology
Hongjie Zheng, Ph.D.	Biostatistics
Marjorie Gatlin, M.D.	Clinical Research
Linda Camera	DRA-CMC
Sharon Olmstead	DRA
Beate Mueller	Project Manager

Meeting Objectives: Discussion points for NDA submission include: electronic assisted format, safety issues, CMC stability and matrix approach, description of clinical studies and data generated by these studies.

Discussion Points: see attached brochure containing outline/discussion points.

Discussion Point 1: NDA format

1. Proposal 1 is for the entire NDA to be submitted in electronic format.

2. Other option is to provide paper copy with sections 11 (data listing) and 12 (case reports) in electronic format.

- ◆ Review copy will be provided on paper; review copies of summaries such as CTR's ISS, ISE will be provided in electronic format. Draft PI will be in MS Word 6.

FDA: We would like safety and efficacy variables data for each patient. 200-300 volumes will be submitted in paper form. Items 11 and 12 will be submitted via electronic format. Statisticians may need more than the SAS file. (The format was discussed with the sponsor after the meeting; a mock-up is pending).

Discussion Point 2: Proposal for SAE narrative descriptions.

- ◆ Provide narratives for all potentially drug related deaths, SAEs and discontinuations due to AE's for all nateglinide treated patients and subjects.
- ◆ Any deaths, SAE's and d/c due to AE's will be provided in tabular form (CTE & ISS).
- ◆ No narratives for patients on other treatments, for pre-randomized patients, and for nateglinide patients involved in elective hospitalization, or accidents due to external causes.

FDA: We will need a narrative description/listing on subjects/patients. If anyone withdraws, we would like a description as to why they left the study. The narrations can be brief, concise. While tabulation form is adequate, a narrative report is more comprehensive. We will accept a listing for everything that is not severe or resulting in death. If there appears to be an association of an adverse event (whether or not serious), additional information will be required. The nature of the event will determine the format.

FDA: ~~Scatograms~~ from laboratory data should be submitted.

Discussion Point 3: Proposal for inclusion of protocol B356, for use in combination with troglitazone.

- ◆ Design would be for Starlix 120 mg, with meals, plus troglitazone 600 mg daily vs. monotherapies and placebo over 24 weeks in type 2 diabetic patients (170 patients per arm);
Important trial for labeling, but not considered a pivotal trial;
Narrative report will be available in time for NDA and for pooling of data in the 120 day NDA safety update;
Except for safety data pooling, information from the study will be analyzed and reported fully in the originally NDA and in the proposed labeling;
SAS transport files will be provided as per proposal number one.

- ◆ Stability Protocol is based upon June 1998 FDA draft guidance.
- ◆ ICH storage conditions and interval (_____)
- ◆ matrix design (plus annual testing) used for commercial packaging configurations.
- ◆ Special stability programs include: _____

◆ For the batch selection: 3 different strengths will be used: 60, 120 and 180 mg; 4 batches of each strength on stability in two different types of packaging, _____ bottles and blisters. Combination of batches manufactured at Novartis East Hanover facility, and the proposed commercial manufacturing site at Novartis, Stein, Switzerland.

FDA: There are some well publicized concerns with troglitazone, so at this time; we cannot lay out a proposal using Starlix and this product. Therefore, we will need to discuss this at a later time.

◆ Product will not qualify for categorical exclusion (21 CFR 25.31(b), therefore, a full EA will be prepared and submitted. This compound is non-toxic and will rapidly biodegrade in the environment, based on toxicology data and evaluation of the structure. It is mostly insoluble in water, however, enough so to enter aquatic compartment.

FDA: Toxicology profiles should be cited and be part of the NDA submission. The proposed stability protocol appears reasonable and adequate. _____ matrix is acceptable.

Questions for the Agency:

1. Under what circumstances would the Starlix NDA be eligible for priority review?

FDA: Mechanism of action is not reason enough to request a priority review. We will first have to evaluate some data before we recommend a priority review. Renal clearance and how much is cleared may also be an important factor.

2. What is the likelihood that this application will go to an Advisory Committee.

FDA: Cannot evaluate or recommend an opinion at this time. The possibility of this NDA being discussed at an Advisory Committee will be determined at the filing meeting.

3. What procedures will yield to a mutually plan to study Starlix in the pediatric population and obtain pediatric exclusivity?

FDA: Novartis is planning to include pediatric studies with a waiver on referrals for post-puberty population. The Agency will look at weight, growth, and insulin levels. Phase 3 studies should help us make a determination on pediatric exclusivity. The sponsor was referred to the AC comments on the use of oral agents in pediatrics.

Minutes Preparer: ISI
3/15/99

Chair Concurrence: ISI
3/15/99

NDA 21-204

No Federal Register Notices were published for this Rx product.

**APPEARS THIS WAY
ON ORIGINAL**

NDA 21-204

No Advisory Committee was assembled to discuss this application.

**APPEARS THIS WAY
ON ORIGINAL**