

**CENTER FOR DRUG EVALUATION AND RESEARCH**

**APPROVAL PACKAGE FOR:**

**APPLICATION NUMBER  
21-204**

**Chemistry Review(s)**

DIVISION OF METABOLISM AND ENDOCRINE DRUG PRODUCTS - HFD-510  
Review of Chemistry, Manufacturing and Controls

NDA 21-204                      Chemistry Review # 1                      Date Reviewed: 02-NOV-2000

Submission Type	Document Date	CDER Rec. Date	Filing Date	U.F. ID #
Original	17-DEC-1999	17-DEC-1999	11-FEB-2000	3853
Amendment	03-AUG-2000	04-AUG-2000		
Amendment	06-SEP-2000	07-SEP-2000		

Applicant: Novartis Pharmaceutical Corporation                      Phone: (973) 781-3570  
59 Route 10                      Fax: (973) 781-3590  
East Hanover, NJ 07936-1080

Drug Product Name                      Proprietary:                      Starlix®  
Nonproprietary/Established/USAN:                      Nateglinide  
Chem. Type/ Ther. Class:                      1 S

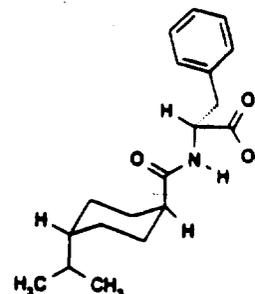
Pharmacological Category/Indication: Hypoglycemic Agent. Adjunct to diet to improve glycemic control in patients with NIDDM whose hyperglycemia cannot be managed by diet alone.

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

Chemical Name, Structural Formula, Molecular Formula, Molecular Weight:

Nateglinide

C<sub>19</sub>H<sub>27</sub>NO<sub>3</sub>  
MW = 317.43  
CAS registry #: 105816-04-4



N-[[*trans*-4-(1-methylethyl)cyclohexyl]carbonyl]-D-phenylalanine or  
(2*R*)-2-[[*trans*-4-isopropyl-cyclohexanecarbonyl]-amino]-3-phenyl-propionic acid

Patent Information: Patent #/ Expiring date/ Type of patent/ Owner/ US Representative  
4,816,484/ 28-MAR-2006/ compound per se and pharmaceutical composition/ Ajinomoto Co. Inc./ Novartis Corp  
5,463,116/ 21-OCT-2012/ compound per se and pharmaceutical composition/ Ajinomoto Co. Inc./ Novartis Corp  
5,488,150/ 30-JAN-2013/ compound per se and pharmaceutical composition/ Ajinomoto Co. Inc./ Novartis Corp

Conclusions & Recommendations: Satisfactory CMC information has been provided to judge the quality of the drug substance, Nateglinide, and the drug product, Starlix® (Nateglinide) Tablets. From the Chemistry viewpoint this application can be approved.

Orig. NDA 21-204  
cc: HFD-510/Division File  
HFD-510/SMalozowaki/SMoore/RSteigerwalt/JWeber/XYsern  
HFD-820/JGibbs

[  ]  
Xavier Ysern, PhD

R/D Init by:

AP

/S/

11/3/00

filename: /nda/21204\_1.doc

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# ORIGINAL

DMF # [redacted] Type II  
A-4166 Manufactured in [redacted]



1. CHEM REVIEW # 2

2. REVIEW DATE: 13-MAR-2000

3. DMF INFORMATION REVIEWED:

Type of Submission	Date of Submission	Location
Amendment	09-JUL-1996	Volume 1.1
Annual Progress Report	13-DEC-1996	Volume 1.1
Annual Progress Report	03-MAY-1999	Volume 2.1
Update (replaces previous submissions)	03-NOV-1999	Volume 3.1 and 3.2

4. PREVIOUS DOCUMENTS:

Type of Submission	Date of Submission	Location	Review
Original	24-OCT-1994	Vol. 1.1	13-JUN-1995

5. NAME & ADDRESS OF DMF HOLDER AND REPRESENTATIVE(S)

DMF HOLDER: Name: [redacted]  
Address: [redacted]  
Phone: [redacted]  
Fax: [redacted]

USA REPRESENTATIVE: [redacted]

6. ITEM REVIEWED

Structural Formula:

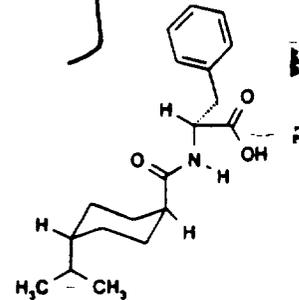
Name: Nateglinide (code name A-4166)

Chemical Formula: C<sub>19</sub>H<sub>27</sub>NO<sub>3</sub>

CAS Number: 105816-04-4

M.W.: 317.43

Chemical Name: *N*-(*trans*-4-Isopropyl cyclohexylcarbonyl)-*D*-phenylalanine or  
(2*R*)-2-[(*trans*-4-isopropyl-cyclohexanecarbonyl)-amino]-3-phenyl-propionic acid



7. DMF REFERENCED FOR:

NDA: 21-204 Original Submission  
Applicant Name: Novartis Pharmaceutical Corporation  
LOA Date: 02-DEC-1999  
Drug Product Name/ Dosage Form: Starlix™ (Nateglinide)/ Tablets  
Strengths/ Route of administration: 60-, 120- and 180-mg/ Oral

8. SUPPORTING DOCUMENTS: None

9. CURRENT STATUS OF DMF/ 10. CONSULTS/ 11. REMARKS/COMMENTS: See next page

12. CONCLUSIONS & RECOMMENDATIONS: *Adequate*. The information submitted in DMF [redacted] is adequate to support the use of A-4166 (nateglinide) as drug substance in the drug product Starlix (Nateglinide) Tablets, under NDA 21-204.

Orig. DMF [redacted] (two copies)  
cc: NDA 21-204  
HFD-510 /MooreS/WeberJ /YsernX  
HFD-820/GibbsJ

Xavier Ysern, PhD  
Review Chemist

NME  
R/D Init. [initials]

filename:/dmf [redacted].doc

[ 3/15/2000 ]

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Division of Metabolism and Endocrine Drug Products

DMF N<sup>o</sup> [redacted] Type II A-4166 Manufactured in [redacted]

Chemistry Review # 1

Date Completed: 8-JUN-1995

DMF HOLDER:

US representative:

phone  
fax

phone  
fax

Product Name: A-4166 (code number)

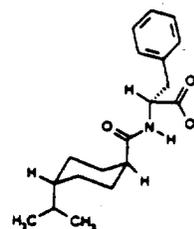
Structural Formula and Chemical Name:

C<sub>19</sub>H<sub>27</sub>NO<sub>3</sub>

M.F. = 317.43

CAS 105816-04-4

N-(trans-4-Isopropyl cyclohexylcarbonyl)-D-phenylalanine



Initial Submission: Doc. 24-OCT-1994 Rec. 25-OCT-1994

Related Documents: IND

REMARKS/COMMENTS: The review of DMF [redacted] is originated by IND [redacted] SDZ DJN 608 15 mg and 30 mg Tablets/ Treatment of Non-Insulin Dependent Diabetes Mellitus) original submission 6-FEB-1995 (rec. 7-FEB-1995). Letter of authorization from [redacted] dated October 24, 1995.

CONCLUSIONS & RECOMMENDATIONS: The information provided in this submission support the use of A-4166 manufactured in [redacted] IND (Phase I studies).

Orig. DMF [redacted] (two copies)  
cc: IND [redacted]  
HFD-510/EKoller/HRhee/JShort/Ysem

R/D Init  
Y-YChiu

~~Xavier Ysem, PhD  
Review Chemist~~

filename [redacted].dmf

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ESTABLISHMENT EVALUATION REQUEST SUMMARY REPORT

Application: NDA 21204/000  
Stamp: 17-DEC-1999 Regulatory Due: 17-OCT-2000  
Applicant: NOVARTIS PHARMS

Priority: 1S  
Action Goal:  
Brand Name: STARLIX (NATEGLINIDE)  
60/120/180MG TABS

Org Code: 510  
District Goal: 18-AUG-2000

Established Name:  
Generic Name: NATEGLINIDE  
Dosage Form: TAB (TABLET)  
Strength: 60-, 120- AND 180-MG

FDA Contacts: X. YSERN (HFD-510) 301-827-6420 , Review Chemist

Overall Recommendation:

ACCEPTABLE on 19-OCT-2000 by M. GARCIA (HFD-322) 301-594-0095

Establishment:

DMF No:  
AADA No:

Profile: CSN OAI Status: NONE  
Last Milestone: OC RECOMMENDATION  
Milestone Date: 19-OCT-2000  
Decision: ACCEPTABLE  
Reason: DISTRICT RECOMMENDATION

Responsibilities:

Establishment: 2416082  
NOVARTIS PHARMA INC (CIBA)  
OLD MILL RD  
SUFFERN, NY 10901

DMF No:  
AADA No:

Profile: TCM OAI Status: NONE  
Last Milestone: OC RECOMMENDATION  
Milestone Date: 18-JAN-2000  
Decision: ACCEPTABLE  
Reason: BASED ON PROFILE

Responsibilities: FINISHED DOSAGE PACKAGER  
FINISHED DOSAGE RELEASE  
TESTER  
FINISHED DOSAGE STABILITY  
TESTER

Establishment: 9692043  
NOVARTIS PHARMA INC (CIBA)  
SCHAFFHAUSERSTRASSE  
CH-4332 STEIN, , SZ

DMF No:  
AADA No:

Profile: TCM OAI Status: NONE  
Last Milestone: OC RECOMMENDATION  
Milestone Date: 26-JUN-2000  
Decision: ACCEPTABLE  
Reason: DISTRICT RECOMMENDATION

Responsibilities: FINISHED DOSAGE  
MANUFACTURER  
FINISHED DOSAGE RELEASE  
TESTER

FDA CDER EES  
ESTABLISHMENT EVALUATION REQUEST  
SUMMARY REPORT

Establishment: 2210396  
NOVARTIS PHARMA INC (SANDOZ)  
59.RT.10  
EAST HANOVER, NJ 079361080

DMF No:  
AADA No:

Profile: TCM OAI Status: NONE  
Last Milestone: OC RECOMMENDATION  
Milestone Date 18-JAN-2000  
Decision: ACCEPTABLE  
Reason: BASED ON PROFILE

Responsibilities: FINISHED DOSAGE PACKAGER  
FINISHED DOSAGE RELEASE  
TESTER  
FINISHED DOSAGE STABILITY  
TESTER

Establishment: 9611204  
NOVARTIS PHARMA INC (SANDOZ)  
LICHSTRASSE 35  
KLYBECK, BASEL, SZ 4002

DMF No:  
AADA No:

Profile: CTL OAI Status: NONE  
Last Milestone: OC RECOMMENDATION  
Milestone Date 24-JAN-2000  
Decision: ACCEPTABLE  
Reason: DISTRICT RECOMMENDATION

Responsibilities: DRUG SUBSTANCE OTHER TESTER

Establishment: 9612715  
NOVARTIS PHARMA INC (SANDOZ)  
RINGASKIDDY/CORK, RINGASKIDD

DMF No:  
AADA No:

Profile: CTL OAI Status: NONE  
Last Milestone: OC RECOMMENDATION  
Milestone Date 18-JAN-2000  
Decision: ACCEPTABLE  
Reason: BASED ON PROFILE

Responsibilities: DRUG SUBSTANCE RELEASE  
TESTER

Establishment: 9614433  
NOVARTIS PHARMANALYTICA SA  
LOCARNO, , SZ

DMF No:  
AADA No:

Profile: CTL OAI Status: NONE  
Last Milestone: OC RECOMMENDATION  
Milestone Date 18-JAN-2000  
Decision: ACCEPTABLE  
Reason: BASED ON PROFILE

Responsibilities: FINISHED DOSAGE STABILITY  
TESTER

Establishment: 2530802  
DMF No:

# ESTABLISHMENT EVALUATION REQUEST SUMMARY REPORT

[

AADA No:

)

Profile: **TCM**                      OAI Status: **NONE**  
 Last Milestone: **OC RECOMMENDATION**  
 Milestone Date: **18-JAN-2000**  
 Decision: **ACCEPTABLE**  
 Reason: **BASED ON PROFILE**

Responsibilities: \_\_\_\_\_

APPEARS THIS WAY  
ON ORIGINAL

APPEARS THIS WAY  
ON ORIGINAL

**ENVIRONMENTAL ASSESSMENT**  
**AND**  
**FINDING OF NO SIGNIFICANT IMPACT**  
**FOR**

**Starlix®**

**(Nateglinide Tablets)**

**60, 120 and 180 mg**

**NDA 21-204**

**Division of Metabolic and Endocrine Drug Products (HFD-510)**  
**Center for Drug Evaluation and Research**

## FINDING OF NO SIGNIFICANT IMPACT

NDA 21-204

Starlix®

(Nateglinide Tablets)

60, 120 and 180 mg

The National Environmental Policy Act of 1969 (NEPA) requires all Federal agencies to assess the environmental impact of their actions. FDA is required under NEPA to consider the environmental impact of approving certain drug product applications as an integral part of its regulatory process.

The Food and Drug Administration, Center for Drug Evaluation and Research has carefully considered the potential environmental impact of this action and has concluded that this action will not have a significant effect on the quality of the human environment and that an environmental impact statement is not required.

In support of their new drug application for Starlix® (Nateglinide Tablets), 60, 120 and 180 mg, Novartis Pharmaceutical Corporation has prepared an environmental assessment (attached) in accordance with 21 CFR Part 25 which evaluates the potential environmental impacts of the use and disposal from use of the product.

This application provides for the indication to improve glycemic control in patients with Type 2 diabetes (non-insulin dependent mellitus, NIDDM) whose hyperglycemia cannot be controlled by diet and physical exercise. Starlix® can be used as monotherapy, and in combination with other oral antidiabetics with a complementary mode of action (such as metformin) when diet, exercise, and Starlix® alone or when diet, exercise, and metformin alone do not result in adequate glycemic control in patients with Type 2 diabetes.

Nateglinide is expected to enter the aquatic environment from use. The compound completely and rapidly biodegrades under aerobic conditions in the aquatic environment. The results of toxicity studies indicate that the compound is not expected to affect organisms at the expected environmental concentrations. Therefore, no adverse environmental effects are expected to result from this action.

Starlix® (Nateglinide Tablets), 60, 120 and 180 mg tablets will be used primarily by patients in their homes and in hospitals and clinics, through physician prescription. Disposal of prescribed drug product will be through use, with returned product disposed through high temperature incineration at licensed disposal facilities. U.S. hospitals, pharmacies, or clinics will dispose of empty or partially empty packages in accordance with their internal waste handling procedures. In the home, disposal will be through community solid waste management systems, which may



c.c. original to NDA 21-204 through J. Weber/HFD-510  
HFD-357/EA File NDA #21-204  
HFD-205/FOI COPY/*Roy Castle*

**REVIEW  
OF  
ENVIRONMENTAL ASSESSMENT  
FOR**

**NDA 21-204**

**Starlix®**

**(Nateglinide Tablets; 60, 120 and 180 mg)**

**Division of Metabolic and Endocrine Drug Products (HFD-510)  
Center for Drug Evaluation and Research**

**Date Completed: August 10, 2000**

## ENVIRONMENTAL ASSESSMENT

**1. Date:**

EA dated: December 8, 1999

PM: Jena Weber

**2. Name of applicant/petitioner:**

Novartis Pharmaceuticals Corporation

ADEQUATE

**3. Address:**

59 Route 10  
East Hanover, New Jersey 07936-1080

ADEQUATE

**4. Description of the proposed action:**

**a. Requested Approval:**

The applicant, Novartis Pharmaceuticals Corporation, has filed NDA 21-204 pursuant to section 505b of the FD&C Act for Starlix® (nateglinide), 60, 120 and 180 mg tablets, packaging in HDPE bottles. An Environmental Assessment (EA) has been submitted pursuant to 21 CFR part 25.

ADEQUATE

**b. Need for Action:**

Starlix® is indicated to improve glycemic control in patients with Type 2 diabetes (non-insulin dependent diabetes mellitus, NIDDM) whose hyperglycemia cannot be controlled by diet and physical exercise.

ADEQUATE

c. **Expected Locations of Use (Drug Product):**

Patients with Type 2 diabetes will use the product in their homes, in clinics and in hospitals. There is no particular geographic region mentioned.

ADEQUATE

d. **Disposal Sites**

Hospitals, pharmacies and clinics will dispose of empty or partially empty packages of drug product according to their internal established procedures. In the home, empty or partially empty containers will typically be disposed of by the community's solid waste management system, which may include landfills, incineration and recycling. Minimal quantities of the unused drug may potentially be disposed of directly into the sewer system.

Rejected materials from the Novartis facility at Suffern, NY are incinerated at the Americal Ref-Fuel (Hempstead) Facility, 600 Avenue C, Westbury, NY 11590. Rejected materials from the Novartis facility at East Hanover, NJ are incinerated at the Novartis Crop Protection Facility, 3905 Highway 75, St. Gabriel, LA 70776.

ADEQUATE

5. **Identification of chemical substances that are the subject of the proposed action:**

**Drug Substance:** The USAN is currently not available. An application is in progress.

**Chemical Name:** N-[[trans-4-(1-methylethyl)cyclohexyl]carbonyl]-D-phenylalanine. (CAS)

(2R)-2-[trans-4-isopropyl-cyclohexanecarbonyl]-amino]-3-phenyl-propionic acid. (IUPAC)

**CAS #:** 105816-04-0

**Molecular Weight:** 317.43

**Molecular Formula:** C<sub>19</sub>H<sub>27</sub>NO<sub>3</sub>

**Structural Formula:** Provided on Page 4 of the EA

ADEQUATE

6. **Environmental Issue:**a. **Identification of Substances of Interest**

The drug, nateglinide, metabolizes significantly. Urinary excretion is the primary elimination route. Studies show that only 16% of the unchanged drug is excreted in urine. The studies show that no metabolites are more potent than nateglinide and the major metabolite (m1) is 5-6 times less potent. Therefore, using the parent compound nateglinide to assess the environmental fate and effects is appropriate.

The firm states that nateglinide is a d-phenylalanine derivative that could be expected to rapidly biodegrade in the environment, probably to the naturally occurring amino acid, phenylalanine, and the cyclohexane species. The phenylalanine species would be expected to rapidly biodegrade, whereas the cyclohexane species would be more persistent. However, investigations of environmental depletion mechanisms demonstrated that nateglinide biodegraded rapidly and significantly (96.4%) in a composite microbial inoculum (containing both effluent and soil microbes) over the course of 28-days at 21°C-22°C.

**ADEQUATE**b. **Environmental Fate of Released Substances: Physical and Chemical Characterization**

<i>Test</i>	<i>Result</i>
Water solubility	pH dependent; pH 5=0.284 g/L, pH 7=2.87 g/L and pH 9=13.2 g/L
Dissociation constant	pKa = 3.1 (21.5-24.3°C)
n-Octanol/water partition coefficient ( $K_{ow}$ )	pH 5 = 331, at pH 7 = 17.3, at pH 9 = 7.32
Vapor pressure	Not expected to be released into the air or have a significant vapor pressure due to the high water solubility
Hydrolysis	Stable at pH 5, 7 and 9, estimated half-life equal to or greater than one year at 25°C
Photolysis	Not discussed; significant biodegradation has been identified below
Aerobic biodegradation	96.4% in 28 days at 21-22°C

The biodegradability data were generated in accordance with GLPs using

an OECD procedure. The test report (refer to Confidential Appendix 11.2.4).

The applicant includes very detailed and scientifically sound test reports that were used to determine the water solubility (Confidential Appendix 11.2.1), dissociation constants (Confidential Appendix 11.2.2), octanol/water partition coefficients (Confidential Appendix 11.2.2), and hydrolysis (Confidential Appendix 11.2.3).

The applicant concludes that the compound is hydrolytically stable at pH 5, 7 and 9 with less than a 10% degradation over a 5-day period. Based on these results, a half-life equal to or greater than one year at 25°C was estimated. According to the guidance for industry entitled Environmental Assessment of Human Drugs and Biologics Applications, dated July 1998, this is not considered a rapid depletion mechanism (criteria for hydrolysis in the guidance is  $t_{1/2}$  (pH 5-9) < or = 24 hours).

The results of the aerobic biodegradation studies revealed that Starlix®, treated at 10 mg C/L, biodegraded significantly (96.46%) in the inoculated water over the 28 day study at 21°C to 22°C. The test system was validated by the reference article, sodium benzoate, which resulted in 93.90% evolved CO<sub>2</sub> over the 28-day study. Aerobic biodegradation in the wastewater treatment process may thus be considered an important environmental depletion mechanism for nateglinide.

#### ADEQUATE

##### c. Environmental concentration

The expected environmental introduction concentration (EIC) is 5.23 ppb based upon an estimated high (most optimistic) quantity to be produced in any of the next 5 years is 231876 kg nateglinide.

Novartis Pharmaceuticals states that they are confident that the actual EIC will not exceed these estimates by an order of magnitude.

#### ADEQUATE

##### d. Environmental Effects:

The environmental effects of nateglinide were evaluated in the aquatic environment following the "Tiered Approach to Fate and Effects Testing" (Figure 1, July 1998 EA guidance for industry). Microbial inhibition was evaluated in accordance with OECD Guideline Number 209. Additionally,

acute toxicity testing was conducted in *Daphnia magna* under and FDA Good Laboratory Practice protocol utilizing Technical Assistance Document (TAD) 4.08 for the US FDA Environmental Assessment Technical Assistance Handbook as a guide.

Microbial inhibition was evaluated by means of an activated sludge-respiration inhibition test, as specified in the OECD Guideline Number 209. The effect of different concentrations of nateglinide was studied on sewage microorganisms by measuring the respiration rate under different conditions. The initial information provided in the original EA dated December 8, 1999 was not clear and did not provide complete information regarding results for the microbial inhibition testing. Therefore, the firm was contacted on July 31, 2000 and a request was made for an amendment that would provide clarification on the results for this test. A fax amendment dated August 2, 2000 was received from the firm and is reviewed below. See following paragraphs for an explanation of these test results for microbial inhibition.

Microbial inhibition was evaluated by means of an activated sludge-respiration inhibition test, as specified in the OECD Guideline Number 209. The effect of different concentrations of nateglinide was studied on sewage microorganisms by measuring the respiration rate under different conditions. The use of a reference substance (3,5-dichlorophenol) in a parallel test allowed for an evaluation of the sensitivity of the microbial population and the adequacy of the test procedures. The median effective concentration ( $EC_{50}$ ) value for 3,5-dichlorophenol was calculated to be 12 mg/L, which is within the acceptable limits (5.0 to 30.0 mg/L), as specified in OECD Guideline 209.

Based on the results of a preliminary range-finding test, nateglinide concentrations of 0.10, 0.32, 1.0, 3.3, and 11 mg/L were tested, and the highest concentration used in the preliminary test, 243 mg/L was retested. Since  $\geq 50\%$  inhibition was not observed at *any* of the concentrations tested, the  $EC_{50}$  value for nateglinide was estimated to be greater than the limit of solubility (i.e.,  $< 10$  mg/L). The highest concentration in both the preliminary and definitive tests, 243 mg/L nateglinide, also resulted in no inhibition of the activated sludge microorganisms. The complete study report is attached as Confidential Appendix 11.2.7.

With a complete and rapid depletion mechanism identified (aerobic biodegradation) and with a non-inhibitory effect on the respiration rate of activated sludge, nateglinide would not be expected to persist in the environment or to disrupt waste treatment processes. According to the "Tiered Approach to Fate and Effects Testing", no further testing is

required. However, a forty-eight hour acute toxicity study was conducted on one suitable test organism (an aquatic invertebrate) to further evaluate the ecotoxicity of the compound. Acute toxicity testing was conducted in *Daphnia magna* under static conditions following the FDA Environmental Assessment Technical Assistance Handbook, Document 4.08. Based on the results of this study, the 48-hour median effect concentration ( $EC_{50}$ ) for nateglinide was estimated to be 320 mg/L and the no-observed-effect-concentration (NOEC) was determined to be 150 mg/L.

The assessment factor may be calculated by dividing an appropriate acute toxicity test endpoint by the MEEC (maximum expected environmental concentration). An assessment factor greater than 1000 would not require additional ecotoxicity testing.

In the case of nateglinide, by applying the 48-hr ( $EC_{50}$ ) from the *Daphnia magna* study (320 mg/L) and the most optimistic calculation of EIC (confidential appendix 11.2.6, 0.005 ppm), an assessment factor of 64,000 is obtained. Thus, no additional ecotoxicity testing would be required for nateglinide. Since the assessment factor calculated for nateglinide is more than one order of magnitude greater than that reported in the guidance document, the results suggest nateglinide would be nontoxic in the aquatic environment.

#### ADEQUATE

#### 7. Mitigation Measures

Based upon the information and data presented in this environmental assessment, Novartis Pharmaceuticals has concluded that no potential adverse environmental impacts are foreseen with the packaging, distribution, use or disposal of Starlix® tablets within the United States. No mitigation measures are considered necessary.

#### ADEQUATE

**8. Alternatives to the proposed action**

No alternatives to the proposed action are suggested, as no potential adverse environmental impacts have been identified for the packaging, distribution, use or disposal of Starlix® tablets will directly benefit patients suffering from Type 2 diabetes (non-insulin dependent diabetes mellitus, NIDDM) whose hyperglycemia cannot be controlled by diet and physical exercise. Therefore, Novartis concludes that approval of this application is therefore, preferable to non-approval.

**ADEQUATE**

**9. List of Preparers**

Environmental testing was conducted by Springborn Laboratories, Inc. in Wareham, Massachusetts. Curriculum vitae, documenting the qualifications and credentials of the contributors to this environmental assessment, are provided in non-confidential appendix I.

**ADEQUATE**

**10. References**

References are provided for the test methods used from the FDA Environmental Assessment Technical Handbook, the environmental assessment guidance for industry, and the organization for economic cooperation and development.

**ADEQUATE**

**11. Appendices**

Confidential appendices containing manufacturing information, production Estimates and test reports are provided.

**ADEQUATE**

The EA is appropriately identified with confidential and nonconfidential sections.



**Endorsements:**

HFD-357/MMaust

/S/

HFD-357/NBSage

/S/

HFD-800/YYChiu

/S/

CC: Original to NDA 21-204 through

EA File 21-204

