CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 21-081

ADMINISTRATIVE DOCUMENTS

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST SUMMARY REPORT

Application: **NDA 21081/000**
Stamp: **23-APR-1999** Regulatory Due: **23-FEB-2000**
Applicant: **HOECHST MARION RSSL**
10236 MARION PARK DRIVE
KANSAS CITY, MO 64137

Priority: **1S** Org Code: **510**
Action Goal: District Goal: **25-DEC-1999**
Brand Name: **LANTUS (INSULIN GLARGINE)INJ 100U/ML**
Established Name:
Generic Name: **INSULIN GLARGINE**
Dosage Form: **INJ (INJECTION)**
Strength: **100 U/ML**

FDA Contacts: **H. RHEE** **(HFD-510)** **301-827-6424** **, Project Manager**
ID = 121714 **, Review Chemist**
S. MOORE **(HFD-510)** **301-827-6430** **, Team Leader**

Overall Recommendation:

ACCEPTABLE on 08-FEB-2000 by M. EGAS (HFD-322) 301-594-0095

Establishment: **9610129**
HOECHST MARION ROUSSEL DEUT
FRANKFURT AM MAIN, , GM
DMF No:
AADA No:

Profile: **CFN** OAI Status: **NONE**
Last Milestone: **OC RECOMMENDATION**
Milestone Date: **08-FEB-2000**
Decision: **ACCEPTABLE**
Reason: **DISTRICT RECOMMENDATION**
Responsibilities: **DRUG SUBSTANCE MANUFACTURER**
FINISHED DOSAGE MANUFACTURER

Profile: **SVS** OAI Status: **NONE**
Last Milestone: **OC RECOMMENDATION**
Milestone Date: **08-FEB-2000**
Decision: **ACCEPTABLE**
Reason: **DISTRICT RECOMMENDATION**

Establishment: **9615000**
HOECHST MARION ROUSSEL DEUT
MARBURG 1
MARBURG, , GM
DMF No:
AADA No:

Profile: **CTL** OAI Status: **NONE**
Last Milestone: **OC RECOMMENDATION**
Milestone Date: **17-MAY-1999**
Decision: **ACCEPTABLE**
Reason: **DISTRICT RECOMMENDATION**
Responsibilities: **DRUG SUBSTANCE RELEASE TESTER**

Establishment: **1913298**
HOECHST MARION ROUSSEL INC
10236 MARION PARK DRIVE
DMF No:
AADA No:

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT

KANSAS CITY, MO 64137

Profile: **SVS** OAI Status: **NONE** Responsibilities: **FINISHED DOSAGE LABELER**
Last Milestone: **OC RECOMMENDATION**
Milestone Date: **11-MAY-1999**
Decision: **ACCEPTABLE**
Reason: **DISTRICT RECOMMENDATION**

Establishmen [redacted]

DMF No:
AADA No:

Profile: **SVS** OAI Status: **NONE** Responsibilities: [redacted]
Last Milestone: **OC RECOMMENDATION**
Milestone Date: **06-MAY-1999**
Decision: **ACCEPTABLE**
Reason: **BASED ON PROFILE**

APPEARS THIS WAY
ON ORIGINAL

USAN

UNITED STATES ADOPTED NAMES COUNCIL

American Medical Association
515 North State Street
Chicago, Illinois 60610

Telefax 312-464-4184
E-mail: Sophia_Fuerst@ama-assn.org

SOPHIA V. FUERST, Associate Secretary
(312) 464-5352

July 28, 1999

LL-87

Quintiles, Inc.
P.O. Box 9708
Mail Station F3-M3026
Kansas City, MO 64134-0708

Attn: Libby Hayes
USAN Liaison for Hoechst Marion Roussel

Dear Ms. Hayes:

It is my pleasure to inform you that the USAN Council adopted **insulin glargine** as the United States Adopted Name for HOE-901; HOE-71GT; Lantus™, Hoechst Marion Roussel, Inc.'s basal insulin analog used in the treatment of diabetes mellitus.

Enclosed is a copy of the Statement of Adoption on **insulin glargine**. Please review this information for accuracy, initial, and return the statement to me within 45 days of the date listed above. After 45 days the information will be submitted to Mosby for publication in the journal of *Clinical Pharmacology and Therapeutics* and to the United States Pharmacopeial Convention, Inc., for publication in the *USP Dictionary of USAN and International Nonproprietary Names*.

Sincerely yours,

Sophia V. Fuerst
Associate Secretary
USAN Council

SF

Enclosure: N99;58

1014

2 1

CDER LABELING AND NOMENCLATURE COMMITTEE

CONSULT # 1203	HFD# 510	PROPOSED PROPRIETARY NAME:	PROPOSED ESTABLISHED NAME:
ATTENTION: William K. Berlin		Lantus	Insulin glargine injection (rDNA origin)
RE: NDA/IND #	21-081		

A. Look-alike/Sound-alike

	Potential for confusion:		
LANTURIL	____ Low	XXX Medium	____ High
LANUM	XXX Low	____ Medium	____ High
BANTHINE	XXX Low	____ Medium	____ High
	____ Low	____ Medium	____ High
	____ Low	____ Medium	____ High

B. Misleading Aspects:

C. Other Concerns:

Confusion with LENTE

D. Established Name

____ Satisfactory

____ Unsatisfactory/Reason

Recommended Established Name

E. Proprietary Name Recommendations:

XXX ACCEPTABLE ____ UNACCEPTABLE

F. Signature of Chair/Date /S/ 8/9/99

APPEARS THIS WAY
ON ORIGINAL

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville MD 20857

Vivian A. Fonseca, M.D.
Tulane University Medical Center
1430 Tulane Avenue, SL 53
New Orleans, Louisiana 70112

NOV 11 1999

Dear Dr. Fonseca:

Between August 23 and August 25, 1999, Mr. Phillip Waldron, representing the Food and Drug Administration (FDA), inspected your conduct of a clinical study (protocol HOE 901/3004) of the investigational drug Lantus (insulin glargine). You conducted this study for Hoechst Marion Roussel, Incorporated. This inspection is part of FDA's Bioresearch Monitoring Program, which includes inspections designed to validate clinical studies on which drug approval may be based and to assure that the rights and welfare of the human subjects of these studies have been protected.

From our evaluation of the inspection report and the documents submitted with that report, we conclude that you adhered to the Federal regulations and/or good clinical practices that govern the conduct of clinical studies and the protection of human subjects.

We appreciate the cooperation shown Mr. Waldron during the inspection. Should you have any questions or concerns regarding this letter or the inspection, please contact me by letter at the address given below.

Sincerely yours,

/S/

Bette L. Barton, Ph.D., M.D.
Chief
Good Clinical Practices Branch I, Room 125
Division of Scientific Investigations
Office of Medical Policy
Center for Drug Evaluation and Research
7520 Standish Place
Rockville, Maryland 20855

APPEARS THIS WAY
ON ORIGINAL

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

Robert E. Ratner, M.D.
650 Pennsylvania Avenue, SE
Suite #50
Washington, DC 20003-4393

OCT 29 1999

Dear Dr. Ratner:

Between August 19 and August 25, 1999, Ms. Christine M. Whitby and Dr. Roy A. Blay, representing the Food and Drug Administration (Agency), inspected your conduct as the investigator of record of your clinical study (Protocol Number HOE 901/3004) of the investigational drug Lantus (insulin glargine injection). You conducted your study for Hoechst Marion Roussel, Inc. This inspection is part of the Agency's Bioresearch Monitoring Program. This program includes inspections to determine the validity of clinical drug studies that may provide the basis for drug marketing approval and to assure that the rights and welfare of the human subjects who participated in those studies have been protected.

At the close of the inspection, Ms. Whitby presented her inspectional observations (Form FDA 483) and discussed these observations with you. From our evaluation of the inspection report, the documents copied during the inspection, and your responses during the inspection to the inspectional observations, we find that you did not adhere to all the pertinent Federal regulations and to an acceptable standard of good clinical practice for the conduct of clinical studies of investigational new drugs and the protection of human subjects. Specifically, we find that:

1. You failed to conduct your study in accordance with the approved protocol [21 CFR 312.53(c)(1)(vi)(a) and 312.60]. In addition, you failed to exercise appropriate control over the investigational drug [21 CFR 312.61].

   Six of the ten subjects _____ enrolled in protocol HOE 901/3004 were dispensed study medication intended for use in protocol HOE 901/3006.

2. You failed to promptly report all changes in research activity to the IRB [21 CFR 312.66].

   The study was terminated in June of 1998; however, the final report of the study was not sent to the IRB until August 6, 1999.

Your letter of August 26, 1999, responds to the items listed on the Form FDA 483. Your explanation of item (1) notes that identical study drugs were used for both protocols and addresses the steps that you have taken to eliminate the possibility of future errors in study drug dispensation. We accept your explanations and acknowledge your assurance that corrective actions will be taken to prevent similar problems in your current and future studies. Your letter has been added to your file. If information is requested from your file in accord with the Freedom of Information Act, our response will include the related correspondence in your file; this serves to give a more complete picture.

We appreciate the cooperation shown Ms. Whitby and Dr. Blay during the inspection. Should you have any questions or concerns regarding this letter or the inspection, please contact me by letter at the address given below.

Sincerely yours,

/S/

Bette L. Barton, Ph.D., M.D.
Chief
Good Clinical Practices Branch I, HFD-46
Division of Scientific Investigations
Office of Medical Policy
Center for Drug Evaluation and Research
Room 125
7520 Standish Place
Rockville, MD 20855

APPEARS THIS WAY
ON ORIGINAL

MEMORANDUM

DATE: March 30, 2000

TO: NDA 21-081

FROM: John K. Jenkins, M.D. /S/ 5/31/00
Acting Director, Division of Metabolic and Endocrine Drug Products, HFD-510

SUBJECT: Overview of NDA Review Issues

Administrative

NDA 21-081 for Lantus (insulin glargine injection [rDNA origin]) was submitted by Aventis Pharmaceuticals (formerly Hoechst Marion Roussel) on April 23, 1999. This NDA was assigned a standard review. The current user fee 12-month date is April 23, 2000.

Clinical/Statistical

Insulin glargine is an analog of human insulin that was created by recombinant DNA technology. Insulin glargine differs from human insulin in that the amino acid asparagine at position A21 is replaced by glycine and two arginines are added to the C-terminus of the B-chain. These changes alter the isoelectric point of insulin glargine and cause it to be less soluble at physiologic pH. This insolubility at physiologic pH results in precipitation of the molecule following injection into the tissue. The formation of these precipitates and the subsequent slow dissolution and absorption is thought to be the basis for the prolonged duration of action of Lantus.

In support of this NDA, the sponsor submitted 6 phase 3 active-controlled trials of Lantus compared to NHP human insulin in patients with Type 1 (Studies 3001, 3004, 3005, and 3003 [pediatric study]) and Type 2 (Studies 3002 and 3006) diabetes. Please refer to the medical review prepared by Dr. Misbin and the statistical review prepared by Dr. Ma for a more detailed analysis of these studies. In all of these studies, patients were randomized to either once daily Lantus in the evening or once or twice daily NPH human insulin as their basal insulin. [redacted]. The primary efficacy endpoint was the change in glycohemoglobin (GHb) from baseline. For each study, the primary endpoint showed no statistically significant difference between Lantus and NPH insulin. While the sponsor did not designate a non-inferiority analysis for the comparison between Lantus and NPH prospectively as should have been done, an analysis of the 95% confidence intervals of the difference in the change from baseline in GHb between Lantus and NPH conducted by Dr. Ma for the four studies conducted in patients with Type 1 diabetes showed that all the intervals included 0 and were within +/- 0.3% GHb. These values are within the +/- 0.3-0.4% margins the division has used in the past for non-inferiority analyses in diabetes studies. It is

important to note that the lack of significant change from baseline to endpoint of GHb in Lantus treated patients provides strong evidence that Lantus is a highly effective insulin since these patients were on insulin at baseline and their glycemic control would have been expected to deteriorate significantly over the course of the study if Lantus had been less effective than NPH. It is also important to note; however, that all these trials were un-blinded and allowed titration of insulin dose to effect and are thus inadequate to support any superiority claims of Lantus over NPH.

The primary adverse events associated with Lantus was hypoglycemia and injection site reactions. The sponsor analyzed hypoglycemia data in many different ways and based on selected analyses would like to make claims in the labeling that Lantus was associated with less hypoglycemia than NPH insulin. As noted by Dr. Misbin, the many analyses of hypoglycemia conducted by the sponsor do not show consistent results and isolated statistically significant findings among multiple post-hoc analyses are not adequate to support a labeling claim.

An unexplained statistically significant increase in progression of diabetic retinopathy in patients treated with Lantus was observed in one study (Study 3006). This finding was not seen in the other studies in which fundic photographs were available for analysis (Studies 3001, 3002, and 3004). These findings were consulted to the Division of Anti-inflammatory, Analgesic, and Ophthalmic Drug Products; please see the consult review prepared by Dr. Chambers. Dr. Chambers recommended that the sponsor conduct a long-term phase 4 study to better characterize the effect, if any, of Lantus on progression of retinopathy. The sponsor has agreed to conduct a 3-year phase 4 study to address this concern and I concur with Drs. Chambers and Misbin that this issue does not warrant delay of approval.

Another issue of clinical concern that was raised in Dr. Misbin's original review was the issue of the potential problems that may occur if Lantus were inadvertently mixed with another insulin in the same syringe. Lantus is formulated at an acidic pH to create a solution; if the acidic Lantus is mixed with another insulin; e.g., regular insulin, in the same syringe the regular insulin will likely precipitate and the PK/PD profile of the regular insulin would thus be altered. Dr. Misbin felt that this was a significant clinical concern [redacted] In response to this concern, the sponsor conducted a PK/PD study in dogs to assess the impact of mixing Lantus with regular insulin in the same syringe before injection compared to injection of the same dose of Lantus and regular insulin by separate injections. The results of this study showed that the PD profile for regular insulin was, on average, slightly delayed when mixed in the same syringe with Lantus compared to separate injections. The sponsor has agreed to include these data in the labeling along with statements in the package insert, patient instructions, and product labels that warn that Lantus should not be mixed with any other insulin in the same syringe. I believe that these labeling and packaging statements are adequate to support approval of the reusable vials of Lantus and to instuct patients and physicians as to the possible adverse consequences of such mixing.

Overall, this NDA is approvable from a clinical/statistical standpoint pending agreement on the final product labeling with the sponsor. These labeling negotiations are ongoing at this time. The sponsor will be reminded in the action letter of their phase 4 commitment to conduct a study to further evaluate the effect, if any, of Lantus on progression of diabetic retinopathy.

Pharmacology/Toxicology

The sponsor conducted an extensive preclinical development program in support of this NDA. For detailed analyses of these studies, please refer to the pharm/tox review prepared by Dr. Rhee and the Team Leader Memo prepared by Dr. Steigerwalt. The general toxicology findings associated with Lantus were primarily those related to hypoglycemia at high doses. Lantus was not genotoxic in a standard battery of assasys; however, in the rat carcinogenicity study, an excess of injection site histiocytomas was observed in male rats. This finding may be related to the vehicle and similar findings were not observed in female rats or in the clinical trials. Nonetheless, this finding will be included in the labeling. In the reproductive toxicity studies, dilatation of the cerebral ventricles was observed in rabbits from two litters of pups from high dose females. This finding warrants a Pregnancy Category C rating for this product.

This application is approvable from a pharmacology/toxicology perspective pending agreement on adequate labeling.

CMC/Microbiology

Please refer to the reviews prepared by Dr. Pardha and Dr. Stinavage for a detailed analysis of the CMC and microbiology information submitted by the sponsor in support of this application. During the course of the review, various deficiencies have been communicated to the sponsor and the responses have adequately addressed the reviewer's concerns. The sponsor has agreed to two CMC phase 4 commitments related to reevaluation of [redacted] once additional long-term stability data are available.

This NDA also covers the OptiPen 1 injection device for administration of insulin from the 3-ml cartridges. This device has been found to be acceptable based on a consult review prepared by CDRH and no preapproval manufacturing inspections are required according to CDRH since this injector is considered to be a Class II medical device.

This NDA is approvable from a CMC standpoint pending agreement on adequate labeling. The sponsor will be reminded of their two CMC phase 4 commitments in the action letter.

Clinical Pharmacology/Biopharmaceutics

Please refer to the review prepared by Drs. Haidar and Fossler for a detailed analysis of the clinical pharmacology and biopharmaceutics studies submitted by the sponsor in support of this NDA. The data submitted by the sponsor demonstrate a "sustained" release PK/PD profile for Lantus following a once-daily injection. The profile is relatively flat and essentially peakless when you look at mean data. No clinically significant difference were observed for PK/PD

when Lantus was injected in the arm, leg, or abdomen. The sponsor did not conduct any formal studies to evaluate the PK/PD of Lantus in special populations (e.g., the elderly, patients with renal impairment); these will be handled by standard language for insulins in the labeling.

This NDA is approvable from a Clinical Pharmacology/Biopharmaceutics perspective pending agreement on adequate labeling. The sponsor has insisted on referring to the PK/PD profile of Lantus as ——— in the labeling.

[; however, to date an agreement has not been reached on the terminology. I have asked Dr. Haidar to look at the PK/PD curves for individual patients to see if they did indeed show no "peak". Depending on the results of this inquiry, a decision will be made on the final wording for the labeling.

DSI/EERs

Audits were completed by the Division of Scientific Investigations of four clinical sites involved in the phase 3 clinical trials. Three of these sites were rated as NAI and one site was rated as VAI. The sponsor adequately addressed the deficiencies noted at the site rated as VAI and the deficiencies noted are not likely to have impacted on the integrity of the data generated.

The EERs were determined to be acceptable for all inspected manufacturing sites as per the report prepared by M. Egas on February 8, 2000.

Labeling

The tradename "Lantus" is acceptable to the division and was found to be acceptable by OPDRA in a consult dated February 29, 2000. The final labeling for the product is currently being negotiated with the sponsor.

Recommendations:

This application should be APPROVED as soon as adequate final labeling can be developed with the sponsor. The sponsor will be reminded of their clinical and CMC phase 4 commitments in the approval letter.

CC:
NDA 21-081
HFD-510 Division File
HFD-510/Jenkins
HFD-510/Malozowski
HFD-510/Weber

APPEARS THIS WAY
ON ORIGINAL

Date: 1/25/00

/S/

From: Saul Malozowski
Medical Team Leader

Subject: Lantos, glargine insulin (NDA 21081). Team leader recommendations

To: John Jenkins
Acting Division Director, DMEDP

This is to support the medical officer recommendation for approval of this product. I will provide some comments on issues that have not been adequately addressed by the sponsor in the submitted documents, but that do not preclude the above-recommended action.

1. Biopharm issues:

In subjects with type 1 diabetes the lack of endogenous insulin secretion allows for the estimation of PD parameters quite easily, because any changes in glucose levels, under controlled conditions, should be the result of the exogenous administered compound. This is not the case in normal volunteers or in subjects with type 2 diabetes, because they secrete endogenous insulin, that may in part affect the glucose levels.

PK determinations, without the benefit of drug specific assays, are more cumbersome in any subject with diabetes. The lack of specific assays has limited our understanding of these parameters in both groups of diabetics. In type 1 we do not know whether the measurements represent the totality of the injected product or part of the injected substance, and in individuals with type 2 it remains unknown whether we are measuring, exogenous, endogenous or a mixture of both insulins.

Until such assays do not become available all parameters related to PK studies will be poorly defined. This concern applies to this and all other design insulins.

2. Mixing

The current formulation does not allow the mixing of this product with other insulins, at all. Currently all other insulins packaged in a vial lend themselves to this maneuver that diminishes the number of injections, increases compliance and potentially improves glycemic control. Although we plan to make patients aware, through the label, that this insulin should not be mixed, we are concerned that this recommendation may not be followed and that patients may, by mistake mix and inject different insulins in the same syringe, resulting in untoward reactions.

3. Retinopathy:

As stated by the MO this issue should be resolved in a phase 4 study. This issue is of the utmost importance. Short studies that suffice for drug approval are not powered to assess complications of this nature that should be weighed against the clear benefit that this product may offer.

4. Tumorogenesis

No information emerged in either the preclinical studies nor in the clinical studies suggest that Lantos may have tumorigenic or carcinogenic properties. It's close relationship with insulin and the chemical modifications that make its IGF-I in vitro activity apparent, leads to the theoretical speculation that compounds of this nature may with time be more potent mitogens that regular insulin is.

No clinical studies will be able to address this issue but we should be aware of this potential complication for this and all other design insulins.

5. Binding

The MO comments on immunogenicity issues are important. Thus, I support the MO position in limiting any claims that emanate from studies using inadequate methodologies.

Conclusion:

I recommend approval of this product pending modifications to the submitted label in order to properly reflect the findings of the studies.

21081 Addendum to Medical Officer's Review
Sponsor's amendment submitted March 2, 2000

A major safety concern is the possible risk of inadvertent mixing of Lantus and regular insulin. Based on data submitted February 9, 2000, we know that Lantus and regular insulin will precipitate if the two solutions are mixed. When equal amounts of Lantus and regular are mixed, 99% of the Lantus and 45% of the regular insulin are precipitated. To evaluate the potential clinical consequences of mixing, we asked HMR to do an experiment in dogs. The results were submitted on 3/2/2000. Based on anaalysis of mean data, HMR concluded that there was no difference between injecting Lantus and regular mixed in the same syringe or injecting them separately. However, I have examined the data based on potential differences in the time to maximal hypoglycemic activity. The results are shown in the table below.

TIME TO LOWEST GLUCOSE

	0.5 hr	1 hr	1.5 hr	2 hr	3 hr	4 hr	5 hr	6 hr +
2 sep	0	2	3	6	3	0	0	0
Mixed	0	0	1	7	4	2	0	0
Regular	0	1	8	4	1	0	0	0
Lantus	0	0	0	0	1	1	5	7

14 dogs in each group were injected with 0.2 U/kg regular insulin and/or Lantus
2 sep = 0.1 U/kg Lantus + 0.1 U/kg regular insulin in separate syringes
mixed = same as above as single injection, both mixed in one syringe

The experiment shows clear separation between Lantus and regular insulin. With Lantus 13/14 dogs had a nadir beyond 3 hours while with regular insulin 13/14 dogs had nadirs before 3 hours. The range of nadir values for 2 separate injections (1-3 hours) is the same as for regular insulin. But the range of nadir values following a single mixed injection appears to be a bit delayed (1.5-4 hours). This is the result that had been expected. However, given the overlap, it is not possible to say if this difference between two separate injections and one injections of mixed insulins is statistically significant. If the true result were a difference of 2/14 dogs having a nadir beyond 3 hours, Dr Sahlroot has determined that a trial should have 48 dogs in each arm to detect the difference (two sided alpha=5%) with 80% power. HMR should be required to repeat the study with 48 dogs in each group.

[redacted] However, if the vials are approved, the label should contain a specific warning that mixing with regular insulin will delay the hypoglycemic activity of the regular insulin.

Labeling Issues:

[redacted] The text on lines 124-131 and tables 1,2 and 3 should be revised to delete reference to [redacted]

Insulin dose: The doses of Lantus and NPH need to be given. These data can be included in the tables or added to the text.

Retinopathy: The text on lines 418-427 is acceptable

Preparation: The following sentence should be added to line 496 in bold type:

[redacted]

/S/

Robert I Misbin MD
HFD 510
March 8, 2000

/S/ 3/31/00

APPEARS THIS WAY
ON ORIGINAL

MAR - 8 2000

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

DATE RECEIVED:	DUE DATE:	OPDRA CONSULT #: 00-0049
March 3, 2000	March 6, 2000	

TO:

John Jenkins, M.D.
Acting Director, Division of Metabolic and Endocrine Drug Products
HFD-510

THROUGH:

Julie Rhee
Project Manager, Division of Metabolic and Endocrine Drug Products
HFD-510

PRODUCT NAME:	MANUFACTURER:
Lantus (Insulin Glargine Injection) 100 units/mL **NDA:** 21-081	Hoechst Marion Roussel, Inc.

SAFETY EVALUATOR: Carol Holquist

OPDRA RECOMMENDATION:

OPDRA has reviewed the proposed insulin pens and provided recommendations for revisions (see review). OPDRA considers this a final review.

/S/ 3/8/2000
Jerry Phillips
Associate Director for Medication Error Prevention
Office of Post-Marketing Drug Risk Assessment
Phone: (301) 827-3246
Fax: (301) 480-8173

/S/ 3/8/00
Peter Honig, MD
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. 15B03
Center for Drug Evaluation and Research

PROPRIETARY NAME REVIEW

DATE OF REVIEW: March 3, 2000

NDA: 21-081

NAME OF DRUG: Lantus™ (Insulin Glargine Injection), 100 units/mL

NDA HOLDER: Hoechst Marion Roussel, Inc.

I. INTRODUCTION:

This consult was written as a follow-up to a pre-approval safety meeting on March 1, 2000 between the Division of Metabolic and Endocrine Drug Products (HFD-510) and OPDRA.

The Division of Metabolic and Endocrine Drug Products (HFD-510) requested a sample of the pens from the sponsor for review and comment.

PRODUCT INFORMATION

Lantus™ is a recombinant human insulin analog that is long acting. It is produced by recombinant DNA technology utilizing a non-pathogenic laboratory strain of *Escherichia coli* (K12) as the production organism. It is indicated for once daily subcutaneous administration (at bedtime) in the treatment of adult and pediatric patients with type 1 diabetes mellitus or adult patients with type 2 diabetes mellitus who require basal (long-acting) insulin for the control of hyperglycemia. Lantus™ is not intended for intravenous administration. The firm has proposed packaging the product in 5 mL and 10 mL vials in addition to a 3 mL cartridge containing 100 units per mL. The cartridges are for use only in OptiPen™ — devices. The medical officer has not recommended the approval of the vials pending results from an animal study on potential consequences of inadvertent mixing of Lantus™ with other insulin products.

II. RISK ASSESSMENT:

After discussion with the Division, the two safety issues remaining were the concerns over mixing Lantus™ with other insulins and the pen device.

A. The firm had not supplied the Division with the results of the animal studies that were requested and therefore could not make a determination on the potential consequences of inadvertent mixing.

OPDRA is concerned about the potential for inadvertent mixing and therefore we strongly recommend the vial, carton and insert be clearly labeled "DO NOT MIX WITH OTHER INSULINS" rather than the proposed "DO NOT MIX". In addition, a statement could be added to the aluminum seal on the vial that states "DO NOT MIX WITH OTHER INSULINS". The

patient, nurse, physician would be able to see this every time the needle is inserted into the diaphragm of the vial.

B. Currently marketed pen devices (NovoPen 3, Humulin N Pen, and Humalog Pen) manufacture only one style pen, which measures 1 unit increments of insulin.

[ ]

In our last review, we recommended the number of the device be included on the pen in conjunction with the name "OptiPen". After further review of the currently marketed pen nomenclature and units of measure, we recommend the number be removed because we believe it may be misinterpreted for the total volume of insulin contained in the cartridge.

[ ]

Lastly, the labeling should be revised to delete any reference to _____ if the firm does not intend to market it in the United States.

APPEARS THIS WAY
ON ORIGINAL

RECOMMENDATIONS:

[redacted] all labeling should be revised accordingly.

OPDRA would appreciate feedback of the final outcome of this consult. We would be willing to meet with the Division for further discussion, if needed. If you have further questions or need clarifications, please contact Carol Holquist at 301-827-3244.

/S/ 3/5/2000

Carol Holquist, RPh
Safety Evaluator
Office of Post-Marketing Drug Risk Assessment

Concur:

/S/ 3/8/2000

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

APPEARS THIS WAY
ON ORIGINAL

NDA 21-081
Office Files
HFD-510; DivFiles; Julie Rhee, Project Manager
HFD-510; John Jenkins, Acting Division Director
HFD-040, Mark Askine, Senior Regulatory Review Officer, DDMAC (Electronic Only)
HFD-440; Lahn Green, Safety Evaluator, DDRE II, OPDRA
HFD-400; Jerry Phillips, Associate Director, OPDRA
HFD-400; Peter Honig, Director, OPDRA (Electronic Only)

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

DATE RECEIVED:	**DUE DATE:**	**OPDRA CONSULT #:** 00-0049
February 8, 2000	March 18, 2000	

TO:

John Jenkins, M.D.
Acting Director, Division of Metabolic and Endocrine Drug Products
HFD-510

THROUGH:

Julie Rhee
Project Manager, Division of Metabolic and Endocrine Drug Products
HFD-510

PRODUCT NAME:	**MANUFACTURER:**
Lantus (Insulin Glargine Injection) 100 units/mL **NDA:** 21-081	Hoechst Marion Roussel, Inc.

SAFETY EVALUATOR: Carol Holquist

OPDRA RECOMMENDATION:

OPDRA has no objections to the use of the proprietary name Lantus™. However, we have reviewed the proposed labels and labeling and provided recommendations for revisions (see review). OPDRA considers this a final review.

/S/

Jerry Phillips
Associate Director for Medication Error Prevention
Office of Post-Marketing Drug Risk Assessment
Phone: (301) 827-3246
Fax: (301) 480-8173

/S/ 2-28-00

Peter Honig, MD
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. 15B03
Center for Drug Evaluation and Research

PROPRIETARY NAME REVIEW

DATE OF REVIEW: February 22, 2000

NDA: 21-081

NAME OF DRUG: Lantus™ (Insulin Glargine Injection), 100 units/mL

NDA HOLDER: Hoechst Marion Roussel, Inc.

I. INTRODUCTION:

This consult was written in response to a request from the Division of Metabolic and Endocrine Drug Products HFD-510 to review the proposed proprietary drug name Lantus™, regarding potential name confusion with existing proprietary/established drug names.

The proprietary name Lantus™, was reviewed and determined to be acceptable by the Labeling and Nomenclature Committee on August 9, 1999.

PRODUCT INFORMATION

Lantus™ is a recombinant human insulin analog that is long acting. It is produced by recombinant DNA technology utilizing a non-pathogenic laboratory strain of *Escherichia coli* (K12) as the production organism. It is indicated for once daily subcutaneous administration (at bedtime) in the treatment of adult and pediatric patients with type 1 diabetes mellitus or adult patients with type 2 diabetes mellitus who require basal (long-acting) insulin for the control of hyperglycemia. Lantus™ is not intended for intravenous administration. The firm has proposed packaging the product in 5 mL and 10 mL vials in addition to a 3 mL cartridge containing 100 units per mL. The cartridges are for use only in OptiPen™ devices. The medical officer has not recommended the approval of the vials pending results from an animal study on potential consequences of inadvertent mixing of Lantus™ with other insulin products.

APPEARS THIS WAY
ON ORIGINAL

II. RISK ASSESSMENT:

The medication error staff of OPDRA conducted a search of several standard published drug product reference texts[1,2,3] as well as several FDA databases[4] for existing drug names which sound alike or look alike to Lantus™ to a degree where potential confusion between drug names could occur under the usual clinical practice settings. A search of the electronic online version of the U.S. Patent and Trademark Office's Text and Image Database was also conducted[5]. An expert panel discussion was conducted to review all findings from the searches. In addition, OPDRA conducted three prescription analysis studies consisting of two written prescription studies (inpatient and outpatient) and one verbal prescription study, involving health care practitioners within FDA. This exercise was conducted to simulate the prescription ordering process in order to evaluate potential errors in handwriting and verbal communication of the name.

A. EXPERT PANEL DISCUSSION

The expert panel consists of members of OPDRA's medication error Safety Evaluator Staff and a representative from the Division of Drug Marketing, Advertising and Communications (DDMAC).

The panel discussed the following sound-alike/look-alike drug names (Anatuss, Anti-Tuss, Lente).

Product Name	Dosage form(s), Generic name	Usual Dose	Observation
Lantus	Injection Insulin glargine injection	Once daily at bedtime	
Anatuss	Oral Solution - OTC 25 mg Phenylpropanolamine, 15 mg Dextromethorphan and 100 mg Guaifenesin	10 mL q6h	*SA
Anti-Tuss	Oral Solution 100 mg/5 mL Guaifenesin	5 to 10 mL q4h not to exceed 2.4 g /day	*SA
Lente	Insulin Zinc Suspension 100 units/mL	Varying dosages	*LA

*SA = Sound-alike
*LA = Look-alike

The panel determined the names identified above had a low potential for confusion with Lantus™ when written and spoken and thus did not pose a significant safety risk.

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[1] MICROMEDEX Healthcare Intranet Series, MICROMEDEX, Inc., 6200 South Syracuse Way, Suite 300, Englewood, Colorado 80111-4740, which includes the following published texts: DrugDex, Poisindex, Martindale (Parfitt K (Ed), Martindale: The Complete Drug Reference. London: Pharmaceutical Press. Electronic version.), Emergindex, Reprodisk, Index Nominum, and PDR/Physician's Desk Reference (Medical Economics Company Inc).

[2] American Drug Index, online version, Facts and Comparisons, St. Louis, MO.

[3] Facts and Comparisons, online version, Facts and Comparisons, St. Louis, MO.

[4] Drug Product Reference File [DPR], the Established Evaluation System [EES], the AMF Decision Support System [DSS], the Labeling and Nomenclature Committee [LNC] database of Proprietary name consultation requests, and the electronic online version of the FDA Orange Book.

[5] WWW location http://www.uspto.gov/tmdb/index.html.

B. PRESCRIPTION ANALYSIS STUDIES

1. Methodology:

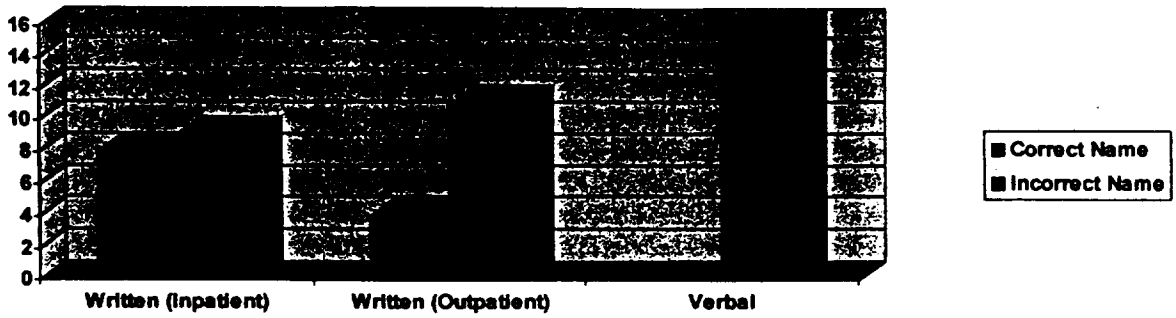
These studies were conducted by OPDRA and involved 92 health professionals comprised of pharmacists, physicians, and nurses within FDA to determine the degree of confusion of Lantus™ with other drug names due to the similarity in handwriting and verbal pronunciation of the name. An inpatient order and outpatient prescriptions were written, each consisting of one known drug product and three unknown drug products and a prescription for Lantus™ (see below). These prescriptions were scanned into a computer and were then delivered to a random sample of the participating health professionals via e-mail. In addition, the outpatient orders were recorded on voice mail. The voice mail messages were then sent to a random sample of the participating health professionals for their interpretations and review. After receiving either the written or verbal prescription orders, the participants sent their interpretations of the orders via e-mail to the medication error staff.

HANDWRITTEN PRESCRIPTION	VERBAL PRESCRIPTION
Outpatient RX: Lantus 10 u #1 vial Sig: 10 u q hs No refill	Lantus 100 units at bedtime, one vial
Inpatient RX: Lantus 10 u QHS	

2. Results:

The results are summarized below:

Study	# of Participants	# of Responses (%)	Correctly Interpreted	Incorrectly Interpreted
Written Inpatient	31	17 (55%)	8	9
Written Outpatient	30	15 (50%)	4	11
Verbal	31	16 (52%)	0	16
Total	92	48 (52%)	12	36



Twenty-five percent of the participants who responded interpreted the name correctly. The majority of verbal respondents provided misspelled variations of the drug name but these were phonetic variations of the name (Lantis rather than Lantus). Misspelled variations were considered incorrect responses. The majority of the outpatient written respondents suggested the drug name was "Lantas" substituting an "a" for the "u". One participant suggested the name Lantus™ could easily be confused with Lasix.

C. SAFETY EVALUATOR RISK ASSESSMENT

1. The inaccurate interpretations of the proposed name identified in the studies did not overlap with any existing approved drug products. The proprietary name does not contain any USAN stems. In addition, the searches conducted within OPDRA did not uncover any additional names that were not discussed by the panel.

2. Lantus™ was designed to compete with NPH insulin, which is now the major insulin formulation that diabetic patients take as "basal" insulin. The absorption of NPH is highly variable and has a maximal effect at about 4-12 hours after injection. It is largely dissipated by 24 hours. Patients with type 1 diabetes use both basal insulin and a short acting insulin (regular or lispro). NPH is given either once per day or twice per day. Lantus™ was designed to be given once per day.

   In trial 3005, Lantus™ was being compared to NPH insulin, when used in combination with Lispro insulin, in patients with type 1 diabetes. Lantus™ was supplied in 5 mL vials and Lispro and NPH were supplied as 10 mL vials. The studies were unblinded because Lantus™ is a clear solution while NPH is a suspension. Patients randomized to Lantus™ were instructed not to mix Lantus™ with lispro. No specific instructions are described for patients randomized to NPH. A 20% reduction in dose of basal insulin occurred in patients switched to Lantus™ from multiple injections of basal insulin. The decrease in basal insulin was partially offset by an increase in Lispro. In this clinical trial "Lantus was confused with Lispro insulin on six occasions and with NPH on one occasion". The medical officer was concerned because Lantus™ is a long acting insulin and is a clear solution and therefore could be confused for short acting insulin. Most long acting insulins are suspensions. NPH insulin can be mixed with regular insulin and injected together in the same syringe. Lantus™ cannot be mixed with regular insulin. The medical officer was concerned about what would happen if a patient mixed Lantus™ with regular insulin and injected the mixture despite warnings not to. He believed such patients would be at risk of delayed hypoglycemia, which would be greatly exacerbated if they took additional insulin to compensate for the perceived lack of effect of the mixture. He recommended the firm produce a distinctive packaging to discourage

confusion with other insulin products or mixing with other insulins and recommended the firm complete animal studies to determine the potential consequences of inadvertent mixing.

After discussion with the medical officer, it was determined that the NPH and Lispro insulins were supplied with their currently marketed labeling. However, he was not sure if Lantus™ was supplied with the proposed labeling or with just an investigational label. He could not determine how the errors occurred.

OPDRA is concerned about this potential confusion especially since these other insulin products are marketed in similar packaging configurations. Novolin R and Humalin R are both available in 1.5 mL cartridges and are clear solutions. Novolin 70/30, Novolin N, Humalin 70/30 are all available in 1.5 mL cartridges and are cloudy milky suspensions. Humalog (Lispro suspension) is available in 3 mL cartridges as a suspension.

OPDRA is concerned about the potential for confusion of inadvertent mixing of these products as well. However, if the product is properly labeled "DO NOT MIX WITH OTHER INSULINS", we believe this would be a satisfactory intervention.

OPDRA is also concerned about confusion of Lispro and Lantus™ since they will both be marketed in 3 mL cartridges and can be utilized in conjunction with one another. The two products were confused six times in clinical trials. The product was supplied in vials but syringes look similar too. OPDRA conducted a search in AERS and uncovered seven reported cases of medication errors involving Humalog and Humulin, resulting in hypoglycemia and hospitilization. Other reports of confusion occurred between Humalin N and Humalin 70/30. There were only two case reports that dealt with confusion with the use of the pen devices. In one case report the patient was utilizing the incorrect pen for the type of insulin cartridge she was trying to administer. In the second case report the patient purchased both a Humulin N Pen and a Humalog Pen. The devices look similar (both gray in color) and as a result the patient injected forty-five units of Humalog instead of the intended Humalin N. The medical officer could not describe the color of the pen device that will be utilized in conjunction with Lantus™.

There is a need to differentiate not only the product labeling for the vials but the pen devices as well. OPDRA has offered some labeling revisions based on the container labels, carton and insert labeling available for review (see below).

LABELING, PACKAGING, AND SAFETY RELATED ISSUES:

In the review of the container labels, carton and insert labeling of Lantus, OPDRA has attempted to focus on safety issues relating to possible medication errors. OPDRA has reviewed the current container labels and carton and insert labeling and has identified several areas of possible improvement, which might minimize potential user error.

A. GENERAL COMMENT

1. It is difficult to determine the color of the pen from the draft labeling. If the pen is gray in color, we recommend the color be revised to differentiate the product from the other insulin cartridge pens, especially since the solution is clear and colorless.

[ ]

B. CONTAINER LABEL (5 mL and 10 mL vials, 3 mL cartridge)

1. Include the following statement on the vial labels in bold print. In addition, if space permits include on the cartridge as well:

   DO NOT MIX WITH OTHER INSULINS.

2. The strength should be relocated to appear in conjunction with the established name so it appears more prominently on the label.

3. —— which appears in conjunction with the net content statement is too prominent and distracts from the actual amount contained in the vial or cartridge and should be deleted.

4. Include the route of administration on the label.

5. The storage information should be on the label since the user may throw away the carton labeling and not know the storing directions for the cartridge.

C. CARTON LABELING (1 x 5 mL vial, 1 x 10 mL vial and 5 x 3 mL)

1. See comments 1, 2, and 3 above.

2. 3 mL cartridge - The following statement should be bolded to increase the prominence:

   For use only in OptiPen® —— devices

3. The statement, "For SQ injection only" could be revised to read, "For subcutaneous injection only".

4. Include the following on the carton:

DO NOT MIX WITH OTHER INSULINS.
Use only if the solution is clear and colorless with no particles visible.

D. INSERT LABELING

DOSAGE AND ADMINISTRATION, Administration – A statement should be included to inform the practitioner that the 3 mL cartridge can only be utilized with the OptiPen ~~—~~ devices as seen on the carton labeling.

E. INFORMATION FOR THE PATIENT INSERT

PREPARING THE LANTUS CARTRIDGE FOR INSERTION INTO THE OPTIPEN ~~——~~
Relocate sentence number five to appear in conjunction with sentence number one.

IV. RECOMMENDATIONS:

A. OPDRA has no objections to the use of the proprietary name Lantus. OPDRA considers this a final review.

B. OPDRA recommends the above labeling revisions that might lead to safer use of the product. We would be willing to revisit these issues if the Division receives another draft of the labeling from the manufacturer.

OPDRA would appreciate feedback of the final outcome of this consult. We would be willing to meet with the Division for further discussion, if needed. If you have further questions or need clarifications, please contact Carol Holquist at 301-827-3244.

/S/ 2/21/00
Carol Holquist, RPhD
Safety Evaluator
Office of Post-Marketing Drug Risk Assessment

Concur:

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

NDA 21-081
Office Files
HFD-510; DivFiles; Julie Rhee, Project Manager
HFD-510; John Jenkins, Acting Division Director
HFD-040, Mark Askine, Senior Regulatory Review Officer, DDMAC (Electronic Only)
HFD-440; Lahn Green, Safety Evaluator, DDRE II, OPDRA
HFD-400; Jerry Phillips, Associate Director, OPDRA
HFD-400; Peter Honig, Director, OPDRA (Electronic Only)

13 & 14. Patent information/Certification

Patent Number: United States Patent No. 5,656,722

Expiration Date: 12 August 2014

Patent Owner: Hoechst Aktiengesellschaft
Frankfurt am Main, Germany

Type of Patent: Drug Substance Patent
Drug Product Patent
Method of use

The undersigned also declares that United States Patent No. 5,656,722 covers insulin glargine, the drug substance of the product for which NDA 21-081 is being submitted for approval in April 1999, as well as any formulation, composition or method of use which employs said drug substance.

This declaration is submitted herewith. Please list the No. 5,656,722 patent in the Orange Book Publication upon approval of the NDA.

Submitted by: J. Michael Nicholas 4/9/99
J. Michael Nicholas, PhD
Director, Marketed Products
US Regulatory Affairs
Hoechst Marion Roussel

APPEARS THIS WAY
ON ORIGINAL

19. FINANCIAL DISCLOSURE

Form FDA 3454 (attached)

Investigator/Subinvestigator list

At the pre-NDA meeting held 8 October 1998, Hoechst Marion Roussel, Inc., made the following proposal to the Agency for studies on which Financial Disclosure information would be collected.

- All Phase III studies
- No Phase II studies. The Phase II studies provide limited efficacy and safety data which will be superseded by the Phase III data. No specific labeling statements will be supported solely by the Phase II studies.
- Selected Phase I studies. Financial disclosure information will be provided for Phase I studies that will be used to support specific statements in the label. While some Phase I studies provide information with respect to the pharmacokinetics/pharmacodynamics of HOE 901, they do not provide specific data that will be used to support the safety or efficacy of HOE 901 in the labeling.

The Agency indicated this proposal "appears to be acceptable". An amendment to the final rule on Financial Disclosure was published on 31 December 1998. This final rule supports the HMR proposal outlined above.

Following the Form FDA 3454 document is a listing of all of the Investigators and Subinvestigators from the Phase III studies (3001, 3002, 3004, 3005 and 3006) and the selected Phase I studies (1004, 1008, 1010, 1012, 1015, 1016, and 1018).

Phase III Studies – Investigator/Subinvestigator list

Study 3001	*19:v1.001:p003.*
Study 3004	*19:v1.001:p008.*
Study 3005	*19:v1.001:p016.*
Study 3006	*19:v1.001:p022.*
Study 3002	*19:v1.001:p032.*

Phase I Studies – Investigator list

Study 1004, 1008, 1010, 1012, 1015, 1016 and 1018	*19:v1.001:p037.*

There was no Financial Disclosure information to report for the investigators who responded to our request for financial disclosure information. Form 3454 has been completed and is attached.

For additional information on these studies, see *Table 8-16, 1:v1.001:p001* and *Table 6-1, 1:v1.001:p001.*

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration

CERTIFICATION: FINANCIAL INTERESTS AND ARRANGEMENTS OF CLINICAL INVESTIGATORS

Form Approved: OMB No. 0910-0396
Expiration Date: 3/31/02

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		
	See attached list of names	

(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
J. Michael Nicholas, Ph.D.	Director, U.S. Regulatory Affairs
FIRM/ORGANIZATION	
Hoechst Marion Roussel, Inc.	
SIGNATURE	**DATE**
J. Michael Nicholas	4/09/99

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

WITHHOLD 35 PAGE (S)

Exclusivity Checklist

NDA: 21-081				
Trade Name: Lantus™				
Generic Name: Insulin glargine injection				
Applicant Name: Aventis Pharmaceutical Inc.				
Division: DMEDP (HFD-510)				
Project Manager: Julie Rhee				
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	x	No	
b. Is it an effectiveness supplement?	Yes		No	x
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	x	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	x	No	
If the answer to (d) is "yes," how many years of exclusivity did the applicant request?	5 years			
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		No	x
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		No	X
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	x	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	Yes		No	x

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.				
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	
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 <u>any one</u> of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)	Yes		No	
If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).				
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		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 #:				
Investigation #2, Study #:				
Investigation #3, Study #:				
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	
Investigation #2	Yes		No	
Investigation #3	Yes		No	
If you have answered "yes" for one or more investigations, identify the NDA in which a similar investigation was relied on:				

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				
Investigation #2				
Investigation #3				
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	Yes		No	
IND#:				
Explain:				
Investigation #2	Yes		No	
IND#:				
Explain:				
Investigation #3	Yes		No	
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	
IND#:				
Explain:				
Investigation #2	Yes		No	
IND#:				
Explain:				
Investigation #3	Yes		No	
IND#:				
Explain:				
c. Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)	Yes		No	
If yes, explain:				

/S/ 2-3-00
Signature of PM/CSO
Date:

/S/ - 4/24/00
Signature of Division Director
Date:

cc:
Original NDA
HFD-510/Division File
HFD-93 Mary Ann Holovac

[redacted]

APPEARS THIS WAY
ON ORIGINAL

INTILES

Quintiles, Inc.
Post Office Box 9708
Kansas City, MO 64134-0708
(816) 767-6000

ORIGINAL

NEW CORRESP
NSE

not /S/
7/12/99

June 10, 1999

Solomon Sobel, M.D.
Director, Division of Metabolic and Endocrine Drug Products
Center for Drug Evaluation and Research (HFD-510)
Food and Drug Administration
Document Control Room 14B-04
5600 Fishers Lane
Rockville, MD 20857

CENTER FOR DRUG EVALUATION AND RESEARCH
RECD
JUN 11 1999
HFD-510

Attention: **Julie Rhee, Project Manager**

Subject: **NDA 21-081**
insulin glargine injection

Request for Marketing Exclusivity for insulin glargine

NAI
/S/
6/18/99

Dear Dr. Sobel,

Quintiles, Inc. as the US Agent for Hoechst Marion Roussel, has been authorized to communicate with the FDA on NDA 21-081.

Enclosed is a letter from Hoechst Marion Roussel, Inc. requesting extended marketing exclusivity for insulin glargine.

If you have any questions regarding the attached document, please do not hesitate to contact me at (816) 767-6674.

Sincerely,

Lavonne Patton

Lavonne M. Patton, Ph.D.
Director, U.S. Drug Regulatory Affairs
Quintiles, Inc.
10245 Hickman Mills Drive
Kansas City, MO 64137

REVIEWS COMPLETED
CSO ACTION:
☐ LETTER ☑ N.A.I. ☐ MEMO
/S/ 7-15-99
CSO INITIALS DATE

7/12/99
/S/

Enclosure

Letter from Hoechst Marion Roussel requesting Marketing Exclusivity

Hoechst Marion Roussel

June 4, 1999

Hoechst Marion Roussel, Inc.

10236 Marion Park Drive
Mail: P.O. Box 9627
Kansas City, MO 64134-0627
Telephone (816) 966-5000
U.S. Web site: www.hmri.com

Solomon Sobel, M.D.
Director, Division of Metabolic and Endocrine Drug Products
Center for Drug Evaluation and Research (HFD-510)
Food and Drug Administration
Document Control Room 14B-04
5600 Fishers Lane
Rockville, MD 20857

Subject: NDA 21-081
insulin glargine

Request for Marketing Exclusivity

Dear Dr. Sobel,

This letter serves as an official request for a period of extended marketing exclusivity under 21CFR 314.50(j) and 21CFR 314.108(b)(2), for insulin glargine (New Drug Application April 9, 1999 and submitted to the Agency on April 22, 1999). As a new chemical entity, insulin glargine is entitled to five (5) years of exclusivity pursuant to 505(j)(4)(D)(ii) of the Federal Food, Drug and Cosmetic Act (21 U.S.C. 355). If you have any questions concerning this request, please contact:

Lavonne Patton, Ph.D.
Quintiles, Inc.
10245 Hickman Mills Drive
Kansas City, MO 64137
Phone: 816 767-6674

Sincerely,

J. Michael Nicholas, Ph.D.
Director, Marketed Products
U.S. Regulatory Affairs
Hoechst Marion Roussel, Inc.
Kansas City, MO 64137

APPEARS THIS WAY
ON ORIGINAL

Hoechst

Hoechst Marion Roussel
The Pharmaceutical Company of Hoechst

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

APPLICATION TO MARKET A NEW DRUG, BIOLOGIC, OR AN ANTIBIOTIC DRUG FOR HUMAN USE

(Title 21, Code of Federal Regulations, 314 & 601)

Form Approved : OMB No. 0910-0338
Expiration Date: April 30, 2000
See OMB Statement on last page.

FOR FDA USE ONLY

APPLICATION NUMBER

APPLICANT INFORMATION

NAME OF APPLICANT	DATE OF SUBMISSION
Hoechst Marion Roussel, Inc.	6/10/99
TELEPHONE NO. *(Include Area Code)* **(816) 966-5000**	FACSIMILE (FAX) Number *(Include Area Code)* **(816) 966-6794**
APPLICANT ADDRESS *(Number, Street, City, State, Country, ZIP Code or Mail Code, and U.S. License number if previously issued)*: **10236 Marion Park Drive, Kansas City, Missouri 64134-0627**	AUTHORIZED U.S. AGENT NAME & ADDRESS *(Number, Street, City, State, ZIP Code, telephone & FAX number)* IF APPLICABLE **Quintiles, Inc. (816) 767-6674 or FAX: (816) 767-7373, P.O. Box 9708, Kansas City, MO 64134-0708**

PRODUCT DESCRIPTION

NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER, OR BIOLOGICS LICENSE APPLICATION NUMBER (If previously issued) NDA 21-081

ESTABLISHED NAME *(e.g., Proper name, USP/USAN name)*	PROPRIETARY NAME *(trade name)* IF ANY	CODE NAME *(If any)*
insuline glargine injection	**LANTUS™**	**HOE 901**

CHEMICAL/BIOCHEMICAL/BLOOD PRODUCT NAME *(If any)*
21^{A}-Gly-30^{B}a-L-Arg-30^{B}b-L-Arg-human insulin

DOSAGE FORM:	STRENGTHS:	ROUTE OF ADMINISTRATION:
Injection	**100 U/mL**	**Subcutaneous**

(PROPOSED) INDICATION(S) FOR USE:
LANTUS™ is an insulin analog indicated for once-daily subcutaneous administration in the treatment of patients with type 1 or type 2 diabetes mellitus who require basal (long-acting) insulin for the control of hyperglycemia.

APPLICATION INFORMATION

APPLICATION TYPE (check one)
☒ NEW DRUG APPLICATION (21 CFR 314.50) ☐ ABBREVIATED APPLICATION (ANDA, AADA, 21 CFR 314.94)
☐ BIOLOGICS LICENSE APPLICATION (21 CFR part 601)

IF AN NDA, IDENTIFY THE APPROPRIATE TYPE ☒ 505 (b) (1) ☐ 505 (b) (2) ☐ 507

IF AN ANDA, OR AADA, IDENTIFY THE REFERENCE LISTED DRUG PRODUCT THAT IS THE BASIS FOR THE SUBMISSION
Name of Drug Holder of Approved Application

TYPE OF SUBMISSION (check one)
☐ ORIGINAL APPLICATION ☐ AMENDMENT TO A PENDING APPLICATION ☐ RESUBMISSION
☐ PRESUBMISSION ☐ ANNUAL REPORT ☐ ESTABLISHMENT DESCRIPTION SUPPLEMENT ☐ SUPAC SUPPLEMENT
☐ EFFICACY SUPPLEMENT ☐ LABELING SUPPLEMENT ☐ CHEMISTRY MANUFACTURING AND CONTROLS SUPPLEMENT ☒ OTHER

REASON FOR SUBMISSION
Request for Marketing Exclusivity for insulin glargine

PROPOSED MARKETING STATUS (check one) ☒ PRESCRIPTION PRODUCT (Rx) ☐ OVER-THE-COUNTER PRODUCT (OTC)

NUMBER OF VOLUMES SUBMITTED_____ THIS APPLICATION IS ☐ PAPER ☐ PAPER AND ELECTRONIC ☐ ELECTRONIC

ESTABLISHMENT INFORMATION

Provide locations of all manufacturing, packaging and control sites for drug substance and drug product (continuation sheets may be used if necessary). Include name, address, contact, telephone number, registration number (CFN), DMF number, and manufacturing steps and/or type of testing (e.g. Final dosage form, Stability testing) conducted at the site. Please indicate whether the site is ready for inspection or, if not, when it will be ready.

See original New Drug Application dated 4/09/99

Cross References (list related License Applications, INDs, NDAs, PMAs, 510(k)s, IDEs, BMFs and DMFs referenced in the current application)

See original New Drug Application dated 4/09/99

PEDIATRIC PAGE

(Complete for all original application and all efficacy supplements)

NDA/BLA Number:	21081	**Trade Name:**	LANTUS (INSULIN GLARGINE)INJ 100U/ML
Supplement Number:		**Generic Name:**	INSULIN GLARGINE
Supplement Type:		**Dosage Form:**	Injectable; Subcutaneous
Regulatory Action:	AP	**Proposed Indication:**	For once-daily subcutaneous administration in the treatment of adult and pediatric patients with type 1 diabetes mellitus or adult patients with type 2 diabetes mellitus who require basal (long-acting) insulin for the control of hyperglycemia.

ARE THERE PEDIATRIC STUDIES IN THIS SUBMISSION?

YES, Pediatric data exists for at least one proposed indication which supports pediatric approval

What are the INTENDED Pediatric Age Groups for this submission?

____NeoNates (0-30 Days) ____Children (25 Months-12 years)

____Infants (1-24 Months) _X_Adolescents (13-16 Years)

Label Adequacy	Adequate for SOME pediatric age groups
Formulation Status	NO NEW FORMULATION is needed
Studies Needed	No further STUDIES are needed
Study Status	

Are there any Pediatric Phase 4 Commitments in the Action Letter for the Original Submission? NO

COMMENTS:

Product is indicated in pediatric patients older than 6 years of age. (2/27/00) 6 and older

APPEARS THIS WAY ON ORIGINAL

This Page was completed based on information from a PROJECT MANAGER/CONSUMER SAFETY OFFICER, JULIE RHEE

/S/

Signature

2-27-00

Date

16. DEBARMENT CERTIFICATION

Hoechst Marion Roussel, Inc. hereby certifies that we did not and will not use in any capacity the services of any person debarred under Section 306(a) or (b) in connection with this application.

J. Michael Nicholas, PhD
Director, Marketed Products
US Regulatory Affairs
Hoechst Marion Roussel

4/9/99
Date

APPEARS THIS WAY
ON ORIGINAL