

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

21-629

ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS

**PATENT INFORMATION SUBMITTED WITH THE
FILING OF AN NDA, AMENDMENT, OR SUPPLEMENT**

**For Each Patent That Claims a Drug Substance
(Active Ingredient), Drug Product (Formulation and
Composition) and/or Method of Use**

NDA NUMBER

21,629

NAME OF APPLICANT / NDA HOLDER

Aventis Pharmaceuticals Inc.

The following is provided in accordance with Section 505(b) and (c) of the Federal Food, Drug, and Cosmetic Act.

TRADE NAME (OR PROPOSED TRADE NAME)

APIDRA

ACTIVE INGREDIENT(S)

Insulin glulisine [rDNA origin]

STRENGTH(S)

100 IU/ml

DOSAGE FORM

10 ml vials

This patent declaration form is required to be submitted to the Food and Drug Administration (FDA) with an NDA application, amendment, or supplement as required by 21 CFR 314.53 at the address provided in 21 CFR 314.53(d)(4). Within thirty (30) days after approval of an NDA or supplement, or within thirty (30) days of issuance of a new patent, a new patent declaration must be submitted pursuant to 21 CFR 314.53(c)(2)(ii) with all of the required information based on the approved NDA or supplement. The information submitted in the declaration form submitted upon or after approval will be the only information relied upon by FDA for listing a patent in the Orange Book.

For hand-written or typewriter versions (only) of this report: If additional space is required for any narrative answer (i.e., one that does not require a "Yes" or "No" response), please attach an additional page referencing the question number.

FDA will not list patent information if you file an incomplete patent declaration or the patent declaration indicates the patent is not eligible for listing.

For each patent submitted for the pending NDA, amendment, or supplement referenced above, you must submit all the information described below. If you are not submitting any patents for this pending NDA, amendment, or supplement, complete above section and sections 5 and 6.

I. GENERAL

a. United States Patent Number 6,221,633 (See attached Notes)	b. Issue Date of Patent 4/24/2001	c. Expiration Date of Patent 6/18/2018
d. Name of Patent Owner Aventis Pharma Deutschland GmbH	Address (of Patent Owner) Industriepark Höchst	
	City/State Frankfurt am Main, Germany	
	ZIP Code D-65926	FAX Number (if available) 011 49 69 305 80556
	Telephone Number 011 49 69 305 6181	E-Mail Address (if available) markus.jacobi@aventis.com
e. Name of agent or representative who resides or maintains a place of business within the United States authorized to receive notice of patent certification under section 505(b)(3) and (j)(2)(B) of the Federal Food, Drug, and Cosmetic Act and 21 CFR 314.52 and 314.95 (if patent owner or NDA applicant/holder does not reside or have a place of business within the United States) ☞ Louis J. Wille	Address (of agent or representative named in 1.e.) Aventis Pharmaceuticals Inc. 1041 Route 202-206 P.O. Box 6800	
	City/State Bridgewater, NJ	
	ZIP Code 08807-0800	FAX Number (if available) 908-231-2691
	Telephone Number 908-231-5721	E-Mail Address (if available) lou.wille@aventis.com

Is the patent referenced above a patent that has been submitted previously for the approved NDA or supplement referenced above?

Yes

No

g. If the patent referenced above has been submitted previously for listing, is the expiration date a new expiration date?

Yes

No

APPEARS THIS WAY
ON ORIGINAL

For the patent referenced above, provide the following information on the drug substance, drug product and/or method of use that is the subject of the pending NDA, amendment, or supplement.

2 Drug Substance (Active Ingredient)

2.1	Does the patent claim the drug substance that is the active ingredient in the drug product described in the pending NDA, amendment, or supplement?	<input checked="" type="checkbox"/> Yes	<input type="checkbox"/> No
2.2	Does the patent claim a drug substance that is a different polymorph of the active ingredient described in the pending NDA, amendment, or supplement?	<input type="checkbox"/> Yes	<input checked="" type="checkbox"/> No
2.3	If the answer to question 2.2 is "Yes," do you certify that, as of the date of this declaration, you have test data demonstrating that a drug product containing the polymorph will perform the same as the drug product described in the NDA? The type of test data required is described at 21 CFR 314.53(b).	<input type="checkbox"/> Yes	<input type="checkbox"/> No
2.4	Specify the polymorphic form(s) claimed by the patent for which you have the test results described in 2.3.		
2.5	Does the patent claim only a metabolite of the active ingredient pending in the NDA or supplement? (Complete the information in section 4 below if the patent claims a pending method of using the pending drug product to administer the metabolite.)	<input type="checkbox"/> Yes	<input checked="" type="checkbox"/> No
2.6	Does the patent claim only an intermediate?	<input type="checkbox"/> Yes	<input checked="" type="checkbox"/> No
2.7	If the patent referenced in 2.1 is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.)	<input type="checkbox"/> Yes	<input type="checkbox"/> No

3 Drug Product (Composition/Formulation)

3.1	Does the patent claim the drug product, as defined in 21 CFR 314.3, in the pending NDA, amendment, or supplement?	<input checked="" type="checkbox"/> Yes	<input type="checkbox"/> No
3.2	Does the patent claim only an intermediate?	<input type="checkbox"/> Yes	<input checked="" type="checkbox"/> No
3.3	If the patent referenced in 3.1 is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.)	<input type="checkbox"/> Yes	<input type="checkbox"/> No

4 Method of Use

Sponsors must submit the information in section 4 separately for each patent claim claiming a method of using the pending drug product for which approval is being sought. For each method of use claim referenced, provide the following information:

4.1	Does the patent claim one or more methods of use for which approval is being sought in the pending NDA, amendment, or supplement?	<input checked="" type="checkbox"/> Yes	<input type="checkbox"/> No
4.2	Patent Claim Number (as listed in the patent)	Does the patent claim referenced in 4.2 claim a pending method of use for which approval is being sought in the pending NDA, amendment, or supplement?	
40		<input checked="" type="checkbox"/> Yes	<input type="checkbox"/> No
4.2a	If the answer to 4.2 is "Yes," identify with specificity the use with reference to the proposed labeling for the drug product.	Use: (Submit indication or method of use information as identified specifically in the approved labeling.) APIDRA is indicated for the treatment of adult patients with diabetes mellitus for the control of hyperglycemia. Copy of proposed labelling is provided in the attached Notes.	

5 No Relevant Patents

For this pending NDA, amendment, or supplement, there are no relevant patents that claim the drug substance (active ingredient), drug product (formulation or composition) or method(s) of use, for which the applicant is seeking approval and with respect to which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner of the patent engaged in the manufacture, use, or sale of the drug product.

Yes

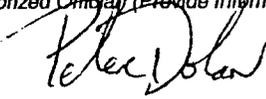
6. Declaration Certification

6.1 The undersigned declares that this is an accurate and complete submission of patent information for the NDA, amendment, or supplement pending under section 505 of the Federal Food, Drug, and Cosmetic Act. This time-sensitive patent information is submitted pursuant to 21 CFR 314.53. I attest that I am familiar with 21 CFR 314.53 and this submission complies with the requirements of the regulation. I verify under penalty of perjury that the foregoing is true and correct.

Warning: A willfully and knowingly false statement is a criminal offense under 18 U.S.C. 1001.

6.2 Authorized Signature of NDA Applicant/Holder or Patent Owner (Attorney, Agent, Representative or other Authorized Official) (Provide Information below)

Date Signed



March 17, 2004

NOTE: Only an NDA applicant/holder may submit this declaration directly to the FDA. A patent owner who is not the NDA applicant/holder is authorized to sign the declaration but may not submit it directly to FDA. 21 CFR 314.53(c)(4) and (d)(4).

Check applicable box and provide information below.

NDA Applicant/Holder

NDA Applicant's/Holder's Attorney, Agent (Representative) or other Authorized Official

Patent Owner

Patent Owner's Attorney, Agent (Representative) or Other Authorized Official

Name
Peter L. Dolan

Address
Aventis Pharmaceuticals Inc.
1041 Route 202-206
P.O. Box 6800

City/State
Bridgewater, NJ

ZIP Code
08807-0800

Telephone Number
908-231-2470

FAX Number (if available)
908-231-2840

E-Mail Address (if available)
peter.dolan@aventis.com

The public reporting burden for this collection of information has been estimated to average 9 hours per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

Food and Drug Administration
CDER (HFD-007)
5600 Fishers Lane
Rockville, MD 20857

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.

INFORMATION AND INSTRUCTIONS FOR FORM 3542a

PATENT INFORMATION SUBMITTED WITH THE FILING OF AN NDA, AMENDMENT OR SUPPLEMENT

General Information

- To submit patent information to the agency the appropriate patent declaration form must be used. Two forms are available for patent submissions. The approval status of your New Drug Application will determine which form you should use.
- Form 3542a should be used when submitting patent information with original NDA submissions, NDA amendments and NDA supplements prior to approval.
- Form 3542 should be used after NDA or supplemental approval. This form is to be submitted within 30 days after approval of an application. This form should also be used to submit patent information relating to an approved supplement under 21 CFR 314.53(d) to change the formulation, add a new indication or other condition of use, change the strength, or to make any other patented change regarding the drug, drug product, or any method of use.
- Form 3542 is also to be used for patents issued after drug approval. Patents issued after drug approval are required to be submitted within 30 days of patent issuance for the patent to be considered "timely filed."
- Only information from form 3542 will be used for Orange Book Publication purposes.
- Forms should be submitted as described in 21 CFR 314.53. An additional copy of form 3542 to the Orange Book Staff will expedite patent publication in the Orange Book. The Orange Book Staff address (as of July 2003) is: Orange Book Staff, Office of Generic Drugs OGD/HFD-610, 7500 Standish Place, Rockville, MD 20855.
- The receipt date is the date that the patent information is date stamped in the central document room. Patents are considered listed on the date received.
- Additional copies of these forms may be downloaded from the Internet at: <http://forms.psc.gov/forms/fdahim/fdahim.html>.

First Section

Complete all items in this section.

1. General Section

Complete all items in this section with reference to the patent itself.

- 1c) Include patent expiration date, including any Hatch-Waxman patent extension already granted. Do not include any applicable pediatric exclusivity. The agency will include pediatric exclusivities where applicable upon publication.
- 1d) Include full address of patent owner. If patent owner resides outside the U.S. indicate the country in the zip code block.

- 1e) Answer this question if applicable. If patent owner and NDA applicant/holder reside in the United States, leave space blank.

2. Drug Substance (Active Ingredient)

Complete all items in this section if the patent claims the drug substance that is the subject of the pending NDA, amendment, or supplement.

- 2.4) Name the polymorphic form of the drug identified by the patent.
- 2.5) A patent for a metabolite of the approved active ingredient may not be submitted. If the patent claims an approved method of using the approved drug product to administer the metabolite, the patent may be submitted as a method of use patent depending on the responses to section 4 of this form.
- 2.7) Answer this question only if the patent is a product-by-process patent.

3. Drug Product (Composition/Formulation)

Complete all items in this section if the patent claims the drug product that is the subject of the pending NDA, amendment, or supplement.

- 3.3) An answer to this question is required only if the referenced patent is a product-by-process patent.

4. Method of Use

Complete all items in this section if the patent claims a method of use of the drug product that is the subject of the pending NDA, amendment, or supplement.

- 4.2) Identify by number each claim in the patent that claims the use(s) of the drug for which approval is being sought. Indicate whether or not each individual claim is a claim for a method(s) of use of the drug for which approval is being sought.
- 4.2a) Specify the part of the proposed drug labeling that is claimed by the patent.

5. No Relevant Patents

Complete this section only if applicable.

6. Declaration Certification

Complete all items in this section.

- 6.2) Authorized signature. Check one of the four boxes that best describes the authorized signature.

Notes to Form FDA 3542a for US Patent No. 6,221,633 for NDA 21,629:

Note to Question 1.a: Aventis Pharma Deutschland GmbH filed a request for reexamination of US Patent No. 6,221,633, which is currently pending before the USPTO. This reexamination application has been assigned, by the USPTO, Reexamination Control No. 90/006928.

Note to Question 2.2: US Patent No. 6,221,633 claims the active ingredient of the drug product APIDRA as a compound, and these claims are not limited to the specific polymorphic forms. However, the patent does not specifically claim any particular polymorph of the active ingredient, and therefore the answer to Question 2.2 is "no".

Note to Question 4.2a: The proposed indications are as follows:

INDICATIONS AND USAGE

APIDRA is indicated for the treatment of adult patients with diabetes mellitus for the control of hyperglycemia.

APIDRA has a more rapid onset of action and a shorter duration of action than regular human insulin. APIDRA should normally be used regimens that include a longer-acting insulin or basal insulin analog. (See WARNINGS and DOSAGE AND ADMINISTRATION.)

APIDRA may also be infused subcutaneously by external insulin infusion pumps. (See WARNINGS, AND PRECAUTIONS, usage in Pumps, Information of Patients, Mixing of Insulins, DOSAGE AND ADMINISTRATION, RECOMMENDED STORAGE.)

**APPEARS THIS WAY
ON ORIGINAL**



Aventis Pharmaceuticals, Inc.
200 Crossing Blvd., P.O.Box 6890
Bridgewater, NJ 08807-0890

Patent Certification

June 18, 2003

Patent Number: United States Patent No. 6,221,633
Expiration Date: June 18, 2018
Patent Owner: Aventis Pharma Deutschland GmbH
Type of Patent: Composition, formulation, method of use

The undersigned declares that United State Patent No. 6,221,633 covers insulin glulisine drug substance of the product for which NDA No. 21,629 is being submitted for approval in June 2003 as well as any formulation, composition or method of use which employs said drug substance.

Please list the No. 6,221,633 patent in the Orange book publication upon approval of the NDA.

A handwritten signature in black ink, appearing to read "Caffé".

Steve Caffé, M.D.
Head, U.S. Regulatory Affairs
Tel. (908) 231 5863 or 3536

NDA 21629
APIDRA (Insulin glulisine, HMR1964)

Aventis, Inc.

patinfo.pdf, pg 1



Aventis Pharmaceuticals, Inc.
200 Crossing Blvd., P.O.Box 6890
Bridgewater, NJ 08807-0890

Patent Information

Patent Number: United States Patent No. 6,221,633
Expiration Date: June 18, 2018
Patent Owner: Aventis Pharma Deutschland GmbH
Type of Patent: Composition, formulation, method of use

EXCLUSIVITY SUMMARY for NDA # 21-629 SUPPL #

Trade Name: ApidraTM

Generic Name Insulin: glulisine [rDNA origin] injection

Applicant Name: Aventis Pharmaceuticals

HFD-510

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 /

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

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

YES / 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.

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

data:

d) Did the applicant request exclusivity?

YES / X / NO / /

If the answer to (d) is "yes," how many years of exclusivity did the applicant request? **5 years**

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

YES / / NO / X /

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

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

YES / / NO / X /

If yes, NDA # _____ Drug Name

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

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

YES / / NO / X /

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

PART II: FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES

(Answer either #1 or #2, as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES /___/ NO / X /

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

NDA #

NDA #

NDA #

2. Combination product.

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

YES /___/ NO /___/

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

NDA #

NDA #

NDA #

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

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

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

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES /___/ NO /___/

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

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

available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

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

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

YES /___/ NO /___/

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

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

YES /___/ NO /___/

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

YES /___/ NO /___/

If yes, explain:

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

YES /___/ NO /___/

If yes, explain:

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

Investigation #1, Study #

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:

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

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

drug product?

Investigation #1 YES /___/ NO /___/

Investigation #2 YES /___/ NO /___/

Investigation #3 YES /___/ NO /___/

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

NDA # _____ Study #

NDA # _____ Study #

NDA # _____ Study #

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

Investigation #__, Study #

Investigation #__, Study #

Investigation #__, Study #

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

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

Investigation #1 !
IND # _____ YES /___/ ! NO /___/ Explain:

!
!
!
!
!
!
!
!
!
!

Investigation #2
IND # _____ YES /___/ ! NO /___/ Explain:

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

Investigation #1
YES /___/ Explain _____ ! NO /___/ Explain _____

Investigation #2
YES /___/ Explain _____ ! NO /___/ Explain _____

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

YES /___/ NO /___/

If yes, explain: _____

Signature of Preparer
Title:

Date

Signature of Office or Division Director

Date

cc:
Archival NDA
HFD- /Division File
HFD- /RPM
HFD-610/Mary Ann Holovac
HFD-104/PEDS/T.Crescenzi

Form OGD-011347
Revised 8/7/95; edited 8/8/95; revised 8/25/98, edited 3/6/00

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

/s/

Julie Rhee
4/16/04 03:20:00 PM

Robert Meyer
4/16/04 03:25:50 PM



Aventis Pharmaceuticals, Inc.
200 Crossing Blvd., P.O.Box 6890
Bridgewater, NJ 08807-0890

Statements of Claimed Exclusivity and Associated Certification

This letter serves as an official request for a period of extended marketing exclusivity under 21 CFR 314.50(j) and 21 CFR 314.108(b)(2), for insulin glulisine. As a new chemical entity, insulin glulisine is entitled for five (5) years of exclusivity.

To the best of applicant's knowledge, a drug has not previously been approved under section 505(b) of the act containing any active moiety in the drug for which the applicant is seeking approval.

**APPEARS THIS WAY
ON ORIGINAL**

PEDIATRIC PAGE

(Complete for all APPROVED original applications and efficacy supplements)

NDA #: 21-629 Supplement Type (e.g. SE5): N/A Supplement Number:

Stamp Date: June 18, 2003 Action Date:

HFD-510 Trade and generic names/dosage form: Apidra (insulin glulisine [rDNA origin] injection)

Applicant: Aventis Pharmaceuticals Therapeutic Class: 1S

Indication(s) previously approved:

Each approved indication must have pediatric studies: Completed, Deferred, and/or Waived.

Number of indications for this application: 1

Indication #1: For the treatment of adult patients with diabetes mellitus for the control of hyperglycemia

Is there a full waiver for this indication (check one)?

- Yes: Please proceed to Section A.
- No: Please check all that apply: Partial Waiver Deferred Completed
* See 11/25/02 pre_NDA meeting minutes
NOTE: More than one may apply
Please proceed to Section B, Section C, and/or Section D and complete as necessary.

Section A: Fully Waived Studies

Reason(s) for full waiver:

- Products in this class for this indication have been studied/labeled for pediatric population
- Disease/condition does not exist in children
- Too few children with disease to study
- There are safety concerns
- Other: _____

If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please see Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section B: Partially Waived Studies

Age/weight range being partially waived:

Min _____ kg _____ mo. _____ yr. 0 Tanner Stage _____
Max _____ kg _____ mo. _____ yr. up to 4 yrs Tanner Stage _____

Reason(s) for partial waiver:

- Products in this class for this indication have been studied/labeled for pediatric population
- Disease/condition does not exist in children
- Too few children with disease to study
- There are safety concerns
- Adult studies ready for approval
- Formulation needed
- Other: _____

If studies are deferred, proceed to Section C. If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section C: Deferred Studies

Age/weight range being deferred:

Min _____ kg _____ mo. _____ yr. 4 Tanner Stage _____
Max _____ kg _____ mo. _____ yr. 17 Tanner Stage _____

Reason(s) for deferral:

- Products in this class for this indication have been studied/labeled for pediatric population
- Disease/condition does not exist in children
- Too few children with disease to study
- There are safety concerns
- Adult studies ready for approval
- Formulation needed

Other: Review adult data first before the initiation of pediatric study

Date studies are due (mm/dd/yy): 12/21/07

If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section D: Completed Studies

Age/weight range of completed studies:

Min _____ kg _____ mo. _____ yr. _____ Tanner Stage _____
Max _____ kg _____ mo. _____ yr. _____ Tanner Stage _____

Comments:

If there are additional indications, please proceed to Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

This page was completed by:

{See appended electronic signature page}

Regulatory Project Manager

cc: NDA
HFD-950/ Terrie Crescenzi
HFD-960/Grace Carmouze
(revised 9-24-02)

Attachment A

(This attachment is to be completed for those applications with multiple indications only.)

Indication #2: N/A

Is there a full waiver for this indication (check one)?

- Yes: Please proceed to Section A.
- No: Please check all that apply: Partial Waiver Deferred Completed
NOTE: More than one may apply
Please proceed to Section B, Section C, and/or Section D and complete as necessary.

Section A: Fully Waived Studies

Reason(s) for full waiver:

- Products in this class for this indication have been studied/labeled for pediatric population
- Disease/condition does not exist in children
- Too few children with disease to study
- There are safety concerns
- Other: _____

If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please see Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section B: Partially Waived Studies

Age/weight range being partially waived:

Min _____ kg _____ mo. _____ yr. _____ Tanner Stage _____
Max _____ kg _____ mo. _____ yr. _____ Tanner Stage _____

Reason(s) for partial waiver:

- Products in this class for this indication have been studied/labeled for pediatric population
- Disease/condition does not exist in children
- Too few children with disease to study
- There are safety concerns
- Adult studies ready for approval
- Formulation needed
- Other: _____

If studies are deferred, proceed to Section C. If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section C: Deferred Studies

Age/weight range being deferred:

Min _____ kg _____ mo. _____ yr. _____ Tanner Stage _____
Max _____ kg _____ mo. _____ yr. _____ Tanner Stage _____

Reason(s) for deferral:

- Products in this class for this indication have been studied/labeled for pediatric population
- Disease/condition does not exist in children
- Too few children with disease to study
- There are safety concerns
- Adult studies ready for approval
- Formulation needed
- Other: _____

Date studies are due (mm/dd/yy): _____

If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section D: Completed Studies

Age/weight range of completed studies:

Min _____ kg _____ mo. _____ yr. _____ Tanner Stage _____
Max _____ kg _____ mo. _____ yr. _____ Tanner Stage _____

Comments:

If there are additional indications, please copy the fields above and complete pediatric information as directed. If there are no other indications, this Pediatric Page is complete and should be entered into DFS.

This page was completed by:

{See appended electronic signature page}

Regulatory Project Manager

cc: NDA
HFD-960/ Terrie Crescenzi
(revised 1-18-02)

FOR QUESTIONS ON COMPLETING THIS FORM CONTACT, PEDIATRIC TEAM, HFD-960
301-594-7337

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

/s/

Julie Rhee

4/15/04 02:38:50 PM



Aventis Pharmaceuticals, Inc.
200 Crossing Blvd., P.O.Box 6890
Bridgewater, NJ 08807-0890

Debarment Certification

June 18, 2003

Aventis Pharmaceutical Inc. hereby certifies that has not used and will not use in any capacity the services of any person debarred pursuant to section 306(a) and (b) of the Federal Food, Drug, and Cosmetic Act [21 U.S.C. 335(a) and (b)] in connection with this application.

A handwritten signature in black ink, appearing to read "Steve Caffé".

Steve Caffé, M.D.
Head, U.S. Regulatory Affairs
Tel. (908) 231 5863 or 3536

Rhee, H Julie

From: Odile.Ernoux@aventis.com
Sent: Friday, April 16, 2004 4:27 PM
To: rheej@cder.fda.gov
Subject: FW: apidra letter received

-----Original Message-----

From: Ernoux, Odile PH/US
Sent: Friday, April 16, 2004 4:21 PM
To: 'rheej@cder.fda.org'
Subject: apidra letter received

Dear Julie,

This mail is to acknowledge receipt of the approval letter for Apidra.

Thanks !

Odile

NDA ACTION PACKAGE CHECKLIST

Application Information

NDA 21-629	Efficacy Supplement Type SE-	Supplement Number: N/A
Drug: Apidra™ (insulin glulisine [rDNA origin] injection)		Applicant: Aventis Pharmaceuticals, Inc.
RPM: Julie Rhee		HFD-510 Phone # 827-6424
Application Type: <input checked="" type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2)		Reference Listed Drug (NDA #, Drug name):
❖ Application Classifications:		
• Review priority:		<input checked="" type="checkbox"/> Standard <input type="checkbox"/> Priority
• Chem class (NDAs only):		IS
• Other (e.g., orphan, OTC)		N/A
❖ User Fee Goal Dates		April 16, 2004
❖ Special programs (indicate all that apply)		<input checked="" type="checkbox"/> None Subpart H <input type="checkbox"/> 21 CFR 314.510 (accelerated approval) <input type="checkbox"/> 21 CFR 314.520 (restricted distribution) <input type="checkbox"/> Fast Track <input type="checkbox"/> Rolling Review <input type="checkbox"/> CMA Pilot 1 <input type="checkbox"/> CMA Pilot 2
User Fee Information		
• User Fee		<input checked="" type="checkbox"/> Paid
• User Fee waiver		<input type="checkbox"/> Small business <input type="checkbox"/> Public health <input type="checkbox"/> Barrier-to-Innovation <input type="checkbox"/> Other
• User Fee exception		<input type="checkbox"/> Orphan designation <input type="checkbox"/> No-fee 505(b)(2) <input type="checkbox"/> Other
❖ Application Integrity Policy (AIP)		
• Applicant is on the AIP		<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
• This application is on the AIP		<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
• Exception for review (Center Director's memo)		
• OC clearance for approval		
❖ Debarment certification: verified that qualifying language (e.g., willingly, knowingly) was not used in certification & certifications from foreign applicants are cosigned by US agent.		<input checked="" type="checkbox"/> Verified
❖ Patent		
• Information: Verify that form FDA-3542a was submitted.		<input checked="" type="checkbox"/> Verified
• Patent certification [505(b)(2) applications]: Verify type of certifications submitted.		21 CFR 314.50(i)(1)(i)(A) <input type="checkbox"/> I <input type="checkbox"/> II <input type="checkbox"/> III <input type="checkbox"/> IV 21 CFR 314.50(i)(1) <input type="checkbox"/> (ii) <input type="checkbox"/> (iii)
• For paragraph IV certification, verify that the applicant notified the patent holder(s) of their certification that the patent(s) is invalid, unenforceable, or will not be infringed (certification of notification and documentation of receipt of notice).		<input type="checkbox"/> Verified

Exclusivity (approvals only)	
• Exclusivity summary	Yes
• Is there an existing orphan drug exclusivity protection for the active moiety for the proposed indication(s)? Refer to 21 CFR 316.3(b)(13) for the definition of sameness for an orphan drug (i.e., active moiety). This definition is NOT the same as that used for NDA chemical classification!	() Yes, Application # _____ (X) No
❖ Administrative Reviews (Project Manager, ADRA) (indicate date of each review)	March 5, 2004
General Information	
❖ Actions	
• Proposed action	(X) AP () TA (X) AE () NA
• Previous actions (specify type and date for each action taken)	
• Status of advertising (approvals only)	(X) Materials requested in AP letter () Reviewed for Subpart H
❖ Public communications	
• Press Office notified of action (approval only)	() Yes (X) Not applicable
• Indicate what types (if any) of information dissemination are anticipated	(X) None () Press Release () Talk Paper () Dear Health Care Professional Letter
❖ Labeling (package insert, patient package insert (if applicable), MedGuide (if applicable))	
• Division's proposed labeling (only if generated after latest applicant submission of labeling)	N/A
• Most recent applicant-proposed labeling	April 15, 2004
• Original applicant-proposed labeling	June 18, 2003
• Labeling reviews (including DDMAC, DMETS, DSRCS) and minutes of labeling meetings (indicate dates of reviews and meetings)	Included
• Other relevant labeling (e.g., most recent 3 in class, class labeling)	NDA 20-563 Humalog and NDA 20-986 NovoLog
❖ Labels (immediate container & carton labels)	
• Division proposed (only if generated after latest applicant submission)	
• Applicant proposed	April 15, 2004
• Reviews	
❖ Post-marketing commitments	
• Agency request for post-marketing commitments	
• Documentation of discussions and/or agreements relating to post-marketing commitments	
❖ Outgoing correspondence (i.e., letters, E-mails, faxes)	Included
❖ Memoranda and Telecons	Included
❖ Minutes of Meetings	
• EOP2 meeting (indicate date)	N/A
• Pre-NDA meeting (indicate date)	Yes (11/25/02)
• Pre-Approval Safety Conference (indicate date; approvals only)	3/29/04
• Other	PreIND (11/7/00)

❖ Advisory Committee Meeting	
• Date of Meeting	N/A
• 48-hour alert	N/A
❖ Federal Register Notices, DESI documents, NAS/NRC reports (if applicable)	N/A
Summary Application Review	
❖ Summary Reviews (e.g., Office Director, Division Director, Medical Team Leader) (indicate date for each review)	
Clinical Information	
❖ Clinical review(s) (indicate date for each review)	AP (4/13/04)
❖ Microbiology (efficacy) review(s) (indicate date for each review)	AP (1/23/04)
❖ Safety Update review(s) (indicate date or location if incorporated in another review)	Yes (page 15 of MOR)
❖ Risk Management Plan review(s) (indicate date/location if incorporated in another rev)	3/12/04
❖ Pediatric Page(separate page for each indication addressing status of all age groups)	Yes
❖ Demographic Worksheet (NME approvals only)	Yes (page 20 of 4/13/04 MOR)
❖ Statistical review(s) (indicate date for each review)	3/16/04
❖ Biopharmaceutical review(s) (indicate date for each review)	3/22/04
❖ Controlled Substance Staff review(s) and recommendation for scheduling (indicate date for each review)	N/A
❖ Clinical Inspection Review Summary (DSI)	
• Clinical studies	Yes(1/29/04)
• Bioequivalence studies	N/A
CMC Information	
❖ CMC review(s) (indicate date for each review)	AE (3/19/04)
❖ Environmental Assessment	
• Categorical Exclusion (indicate review date)	Granted (3/19/04)
• Review & FONSI (indicate date of review)	
• Review & Environmental Impact Statement (indicate date of each review)	
❖ Microbiology (validation of sterilization & product sterility) review(s) (indicate date for each review)	1/23/04
❖ Facilities inspection (provide EER report)	Date completed: 3/30/04 (X) Acceptable () Withhold recommendation
❖ Methods validation	() Completed () Requested (X) Not yet requested
Nonclinical Pharm/Tox Information	
❖ Pharm/tox review(s), including referenced IND reviews (indicate date for each review)	AP (2/25/04) IND 61,956
❖ Nonclinical inspection review summary	N/A
❖ Statistical review(s) of carcinogenicity studies (indicate date for each review)	N/A
❖ CAC/ECAC report	N/A

27 page(s) of
revised draft labeling
has been redacted
from this portion of
the review.



April 15, 2004

Dr. David Orloff
Director, Division of Metabolic and Endocrine Drug Products (HFD-510)
Center for Drug Evaluation and Research
Food and Drug Administration
Central Document Room 14B-19
5600 Fishers Lane
Rockville, MD 20857

**NDA 21-629: APIDRA™
HMR 1964 – Insulin glulisine (rDNA human insulin analog)
Pediatric Study Deferral and Partial Waiver Request**

Dear Dr. Orloff:

Reference is made to IND 61,956 (HMR 1964 – rDNA human insulin analog) and to the above-mentioned New Drug Application (NDA) for APIDRA™ (HMR 1964 – insulin glulisine), which was submitted to the Agency on June 18, 2003. Reference is also made to the official minutes of the pre-NDA meeting held on November 25, 2002. For your convenience, the above-referenced minutes have been included with this correspondence as an *Attachment*.

The purpose of this April 15, 2004 correspondence is to request the following, in accordance with Section 2 of the Pediatric Research Equity Act: 1) a deferral of the requirement to submit an assessment of APIDRA™ in the pediatric population and 2) a partial waiver of the requirement to submit an assessment of APIDRA™ in children under 4 years of age.

Rationale for Deferral Request

Aventis plans to investigate APIDRA™ in the pediatric population. A 26-week, multicenter, open, parallel clinical trial has been designed to study the efficacy and safety of insulin glulisine compared with insulin lispro in children and adolescents (4-17 years of age) with type 1 diabetes mellitus. The primary objective of this trial is to demonstrate non-inferiority of insulin glulisine compared to insulin lispro in the change in GHb from baseline to endpoint in the above-mentioned pediatric population, with endpoint defined as the subject's last available measurement after start of treatment.

On June 18, 2003, the NDA for APIDRA™ was submitted to the Agency. In addition, data from study 3011 were submitted to the Agency on November 4, 2003 as part of the 120-day safety update for APIDRA™. Having

first submitted the NDA and extension study data, in following the recommendation of the Division, we filed the pediatric protocol to the IND for HMR1964 on December 11, 2003 (Serial No. 110) for Agency review. Aventis plans to initiate the pediatric study as soon as possible following receipt of feedback from the Agency. We anticipate study initiation to take place mid-year 2004 and the clinical study report to be available for submission to the FDA by December 21, 2007. Because of our clear plans to conduct the above-mentioned clinical study as soon as possible, therefore, Aventis requests a deferral of submission of the pediatric study assessment.

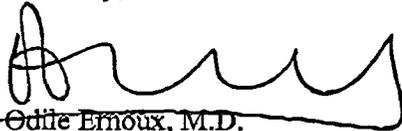
Rationale for Partial Waiver Request

Aventis believes that the number of type 1 diabetes patients under age 4 is such a small population that conducting clinical trials in this age subgroup will be extremely difficult and impractical. Furthermore, it is highly unlikely that APIDRA™ will be used by a substantial number of pediatric patients under 4 years of age. Given the above-mentioned rationale, therefore, Aventis is seeking a partial waiver for conducting clinical studies in this age subgroup.

This submission is fully electronic and provided on the enclosed CD. Aventis certifies that all electronic media have been scanned and found to be free of any known computer viruses (Norton AntiVirus Corporate Edition; program 7.50.846, Scan Engine 4.1.0.6, Version 60412h, April 12, 2004). In addition, an original signed Cover Letter and Form FDA 356h are provided in paper form.

Aventis Pharmaceuticals Inc. looks forward to working with the Division to facilitate the review of the APIDRA™ NDA. Should you have any questions regarding this material, please contact the undersigned by telephone at (908) 231-3536 or by fax at (908) 304-6318 or, in my absence, please contact Steve Caffé, M.D. by telephone at (908) 231-5863.

Sincerely,



Odile Ernoux, M.D.
Director, Regulatory Affairs
Aventis Pharmaceuticals, Inc.
Phone: (908)-231-3536
Fax: (908)-304-6318

Attachment: 1

Attachment

MEMORANDUM OF MEETING MINUTES

MEETING DATE: November 25, 2002
TIME: 10:00 – 11:30 am
LOCATION: Parklawn 3rd floor c/r "Chesapeake"
APPLICATION: IND 61,956 HMR 1964 (rDNA human insulin analog)
TYPE OF MEETING: Pre-NDA meeting
MEETING CHAIR: David Orloff, M.D., Director, DMEDP
MEETING RECORDER: Julie Rhee, Regulatory project Manager, DMEDP

FDA ATTENDEES, TITLES, AND OFFICE/DIVISION:

Name of FDA Attendee	Title	Division Name & HFD#
David Orloff, M.D.	Director	Division of Metabolic and Endocrine Drug Products, HFD-510
Joanna Zawadzki, M.D.	Medical Officer	DMEDP
Stephen Moore, Ph.D.	Chemistry Team Leader	DMEDP
Xavier Ysern, Ph.D.	Chemist	DMEDP
Pat Cricenti	Chief, General Hospital Devices Branch	Center for Device and Radiological Health (CDRH)
Herman Rhee, Ph.D.	Pharmacologist	DMEDP
Todd Sahlroot, Ph.D.	Statistical Team Leader	DB2 (HFD-715)
Lee Pian, Ph.D.	Statistician	DB2 (HFD-715)
Jim Wei, Ph.D.	Biopharm Reviewer	DMEDP
Justina Molzon, M.S., J.D.	Associate Director for International Program	CDER
Gary Gensinger	Review Technology	CDER
Patrick Guinn	Project Manager	Office of Drug Safety (ODS)
Joslyn Swann	Safety Evaluator	ODS
Denise Toyer	Safety Evaluator Team Leader	ODS
Alina Mahmud	Safety Evaluator Team Leader	ODS
Julie Rhee	Regulatory Project Manager	DMEDP

EXTERNAL CONSTITUENT ATTENDEES AND TITLES: Aventis Pharmaceuticals, Inc.

External Attendee	Title
Odile Ernoux, M.D.	Regulatory Affairs Liaison, Head of Endocrine and Metabolism Products
Chanda Moseley, Ph.D.	Regulatory Affairs Liaison
Paul Walrant, Ph.D.	Regulatory Affairs Coordination
Gary Ruezinsky, M.S.	Regulatory Affairs CMC

Rosemary Crew, M.S.	Regulatory Affairs Publishing
Ralf Roskamp, M.D.	Endocrine and Metabolism Products, Vice-President
Fred Senatore, M.D.	Global Project Leader
Nicholas Milner, Ph.D.	Global Project Manager
Kirk Ways, M.D., Ph.D.	Global Clinical Manager
Elisabeth Souhami, M.D.	Clinical Manager
Lynne Griffiths, Ph.D.	Medical Writer
Anne Frick, Ph.D.	Pharmacokinetics
Reinhard Becker, M.D., Ph.D.	Clinical Pharmacology
Robert Costello, Ph.D.	Biostatistician
Debbie Zielensky, Ph.D.	Data Management
Ray Zhu, Ph.D.	Biostatistician
Gerhard Seipke, Ph. D.	General Preclinical Matters
Ingo Stammberger, Ph.D.	Toxicologist
Peter Boderke, Ph.D.	Pharmaceutical Sciences
Annette Schlaefer, M.S.	Analytical Sciences
Claus Tollnick, Ph.D.	Process Development

BACKGROUND:

HMR 1964 is a _____

The NDA is to include the following presentations:

- 10 mL vials,
- _____
- _____
- _____

The sponsor also plans to make a claim for the use of solution from vials in approved external pumps manufactured by Disertronic and MiniMed.

The NDA is expected to be submitted at the end of May 2003.

The background material for this pre-NDA meeting was received on October 28, 2002.

DISCUSSION POINTS:

General / Clinical questions

1. **Aventis will appreciate any comments on the proposed table of contents, in particular for Module 1.**

FDA's response:

- i. *The Division does not have any specific comments. However, risk management is required at the end of Module 1 in the NDA.*
- ii. *The Office of Drug Safety gave a copy of the attached document on risk management to the sponsor.*
- iii. *The Division of Medication Errors and Technical Support (DMETS) encouraged the sponsor to include any supporting information pertaining to the selection of their proposed proprietary name.*

2. **Does the Agency have any specific recommendations or requests concerning the electronic-only submission, which will ease the review?**

FDA's response:

- i. *Provide a hard copy for the device portion of the NDA to CDRH since CDRH does not have access to electronic document. The sponsor agreed to do so.*
- ii. *Dr. Zawadzki discussed specific review recommendations and gave a list of these recommendations to the sponsor in the attached "Comments for Sponsor 11/25/02".*
- iii. *For clinical safety data, it is acceptable to pool data from patients with type 1 diabetes only. For efficacy, data should be separated for patients with type 1 diabetes and for type 2 diabetes. In addition, the sponsor stated that they are willing to pool the efficacy data for type 1 and type 2 diabetes if the Division wants the pooled data. The Division responded that they will leave this decision to Aventis.*

3. **Does the Agency agree with the proposed approach concerning Data Correction Form, Bookmarking/Hyperlinking?**

FDA's response: Yes.

4. Does the Agency accept the proposal of providing Financial Disclosure documents for phase III trials only?

FDA's response: Yes.

5. Does the Agency agree that for the Environmental Assessment, this application qualifies for categorical exclusion?

FDA's response: Yes.

6. Does the Agency agree that the Population Exposure is adequate to file the application?

FDA's response: Yes. Although there are sufficient data to file the application, it would be helpful to have additional safety data on hypoglycemic and cardiac events. These safety data are going to be asked during the review of the NDA.

7. Does the Agency concur with the reporting plans for the 120-day safety update?

FDA's response: Yes. Refer to the above FDA's response (item #6). The reporting plan is to include 6-month data (about 700 patients exposed to drug product) in NDA and the 120-day safety update is to include extension data. All efficacy data is to be included in the NDA at the time of NDA submission.

8. Does the Agency agree that, given the contents and format of the clinical sections of Module 2 (Overview, SCE and SCS), no ISS or ISE in the previous format is needed for this application?

FDA's response: The sponsor is still required to submit information on ISE and ISS in Module 2. However, if ISE and ISS cannot be fitted in Module 2, they could be included in Module 5.

9.

[Redacted text]

10. Does the Agency concur with the proposal that only the CRFs for subjects who died or discontinued a study as a consequence of an adverse event, and CRFs for cases of

pregnancy will be included in the submission?

FDA's response: Yes. It is acceptable to submit CRFs for patients who died or discontinued a study. Either CRFs or narratives for all severe hypoglycemic episodes, specially hypoglycemic events requiring a third party intervention or glucose level of less than 36 mg/ml, motor vehicle accidents, or other serious adverse events associated with hypoglycemia, or severe nocturnal hypoglycemia, should be provided.

11. Does the Agency concur with the plans not to include Patient Profiles in this electronic submission?

FDA's response: Yes.

12. Does the Agency concur with the plan not to submit a separate document equivalent to the former Item 10 (statistical) in this electronic submission?

FDA's response: Yes.

The sponsor stated that protocols and randomization will be included in the individual study report under Module 5. The sponsor also stated that hard copies of phase 3 study reports and protocols are to be submitted at the time of NDA submission.

13. Does the Agency accept the proposal to provide as a separate package, in a SAS transport format (.XPT), the SAS analysis data sets and programs for phase III studies?

FDA's response: Submit SAS program for phase 3 studies as Ascii file.

CMC questions:

1. Does the Agency consider the organization and contents of the Table of Contents of the CMC sections (Module 2-section 2.3, and Module 3) acceptable?

FDA's response: Yes. The 1996 guidance document on content and format for biotech product is recommended for presentation of the detailed information under the various CTD headings.

2. Does the Agency agree with the plans concerning Drug Substance process validation and/or evaluation?

FDA's response: Yes. However, any differences between the NDA batches and commercial

batches need to be described in the NDA.

3. Are the proposed specifications for Drug Substance acceptable?

FDA's response: The data source of batches is acceptable for setting specifications. The specifications appear to be acceptable. However, the final determination of the adequacy of the specifications is a review issue.

4. Does the Agency agree with the strategy concerning Drug Substance stability?

FDA's response: Yes. The stability data can be updated during the review period. Any extension will be based on actual stability data and may be extrapolated up to 6 months beyond available real time data (e.g., 24 month retest requires 18 month real time data).

5. Does the Agency agree with the plans concerning Drug Product process validation and/or evaluation?

FDA's response: Yes.

6. Does the Agency agree with the strategy concerning the Drug Product batch size plans?

FDA's response: Yes. However, approval of the NDA will be based on the data available in the NDA. If _____ data is presented, the scale approved will be _____. A comparability protocol can be used for scale-up from pilot scale batches to commercial batches to reduce the filing category.

7. Are the proposed specifications for Drug Product acceptable?

FDA's response: Yes. The data source of batches is an acceptable basis for setting specifications. However, the final determination of the adequacy of the specifications is a review issue.

8.

9.

10. Does the Agency agree with the strategy concerning Drug Product stability?

11. Does the Agency accept the testing strategy concerning Drug Product sterility?

FDA's response: Yes.

12. Does the Agency agree that the proposed program on external pumps, namely compatibility studies already provided in the IND and new investigations on leachables, to be provided in section 3.2.R, is sufficient for the NDA?

FDA's response:

- i. A decrease in m-cresol is noted to occur in the pump studies. The sponsor needs to support preservative effectiveness.*
- ii. There is a concern since insulin contains m-cresol ————— M-cresol is a solvent with potential to leach out catheter components during the in-use period. The sponsor responded that they plan to do a study on leachables using placebo with all ingredients except insulin because insulin masks some leachables peaks. The sponsor*

indicated they had a partial copy of the draft guidance document dated February 20, 1985 and titled "REQUIREMENTS PROPOSED FOR PUMP INSULINS AND INSULIN PUMPS". A complete copy is to be provided to the sponsor.

iii. The Division asked if the sponsor has an established name for the drug product. The sponsor responded that they have taken steps to get acceptance of the name by USAN.

Pediatric program:

1.

[Redacted]

2.

[Redacted]

3.

[Redacted]

IND 61,956
11/25/02 pre-NDA meeting minutes
Page 9

Handouts:

1. Office of Drug Safety comments on risk management
2. CTD submission
3. Comments for Sponsor 11/25/02
4. DRAFT REQUIREMENTS PROPOSED FOR PUMP INSULINS AND INSULIN PUMPS (dated Feb 20, 1985)

MEETING MINUTES

The Sponsor is encouraged to evaluate the risk with use of the product and propose ways to manage or reduce these risks. Plans for risk management should be included in Module I of the Common Technical Document for the NDA application.

If the NDA application is not being submitted in the Common Technical Document, plans for risk management should be included in the Clinical Section.

APPEARS THIS WAY
ON ORIGINAL

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: April 15, 2004

TO: File, NDA 21-629, APIDRA (insulin glulisine)

FROM: K. Eddie Gabry, MD, Medical Officer

SUBJECT: Review of Financial Disclosure in original NDA
NDA 21-629, APIDRA (Insulin glulisine) Injection

At the time of this NDA submission, a single investigator, _____ disclosed "significant payments of other sorts" exceeding \$25,000 cumulative "during the course of the study and one year after". A descriptive statistical analysis comparing the HbA1c results at the _____ (~3% of patients in the trials) for studies _____ and _____ was unrevealing of any inconsistencies that might lead the team to question the integrity or validity of the data from that site or from the trial generally.

APPEARS THIS WAY
ON ORIGINAL

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

/s/

Kamal Gabry
4/15/04 04:39:44 PM
MEDICAL OFFICER

David Orloff
4/16/04 03:25:25 PM
MEDICAL OFFICER

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: April 8, 2004

TO: David Orloff, M.D., Director
Division of Metabolic and Endocrine Drug Products
HFD-510

VIA: Julie Rhee, Regulatory Health Project Manager,
Division of Metabolic and Endocrine Drug Products
HFD-510

FROM: Jeanine Best, M.S.N., R.N., P.N.P.
Patient Product Information Specialist
Division of Surveillance, Research, and Communication Support
HFD-410

THROUGH: Gerald Dal Pan, M.D., M.H.S., Director
Division of Surveillance, Research, and Communication Support
HFD-410

SUBJECT: ODS/DSRCS Review #2 of the Patient Labeling for Apidra
(insulin glulisine [recombinant DNA origin] injection),
NDA 21-629

Background and Summary

The sponsor submitted revised labeling dated April 6, 2003, including revised Patient Information and *Instructions for Use* for Apidra (insulin glulisine [recombinant DNA origin] injection), NDA 21-629. ODS/DSRCS provided comments on the original submitted patient labeling for this product. Please refer to our consult dated January 15, 2004.

We have the following comments and recommendations:

1. The April 6, 2004, revised Patient Information has a Flesch-Kincaid Reading Level of 12.0 (likely higher than 12th grade as this scale does not record scores above the 12th grade), and a Flesch Reading Ease Score of 30.1. Optimally, the reading level should be between the 6th and 8th grade, and the reading ease should be 60% or above (60% corresponds to an 8th grade reading level. Approximately 50% of U.S. adults function at a lower literacy level and read at less than an 8th grade level. The American Public Health Association reports in their April 1, 2004, article, *Disparities in Health Literacy* that:
 - "Over half of people living in the United States are affected by health literacy."
 - "Two thirds of U.S. adults age 60 and over have inadequate or marginal literacy skills,

and 81 percent of patients age 60 and older at a public hospital could not read or understand basic materials such as prescription labels."

- "Approximately half of welfare recipients read below the fifth-grade level."
- "Up to 40% of African-Americans have problems reading."
- "Diabetes patients with poor literacy are more likely to have poorly controlled blood sugar and serious long-term complications."

We question the usefulness of the revised Patient Information as an appropriate risk communication tool for a broad range of patients, including those with lower literacy. We recommend that the sponsor test their Patient Information for comprehension using a sample of patients that includes an adequate number of those with lower literacy levels.

2. There are many opportunities in the Apidra PPI to lower the reading level, thereby increasing the comprehension to a broader range of patients:
 - simplify words and statements and decrease sentence length throughout
 - Pictures and/or diagrams to demonstrate and reinforce the particular direction should always accompany *Instructions for Use*.
 - Avoid the presentation of information in a table format, unless carefully explained to the patient. Lower literate patients cannot interpret data presented in tables.
3. ODS/DSRCS continues to note that existing PPIs for diabetic products are quite varied and most are written at a reading comprehension level that is too high to be understood by lower literacy readers. The review division may want to consider initiating class PPI labeling for diabetic products utilizing the following suggestions:
 - Follow a question and answer format with the contents ordered similarly to Medication Guides. Alternative formats are discouraged without supportive data for their communication effectiveness from studies such as label comprehension testing.
 - Simplify the vocabulary and sentence structure for lower literacy readers. A 6th to 8th grade reading comprehension level is optimal for all patient materials.
 - Keep information on the medical conditions brief. Patient information leaflets (PPIs) are to enhance appropriate use of medications and provide important risk information. Education of underlying medical conditions should be separated.
 - Remove any promotional language per DDMAC guidelines.

Please let us know if you have any questions.

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

/s/

Jeanine Best
4/8/04 11:51:08 AM
DRUG SAFETY OFFICE REVIEWER

Gerald DalPan
4/8/04 02:22:43 PM
MEDICAL OFFICER

Rhee, H Julie

From: Rhee, H Julie

Sent: Wednesday, April 07, 2004 5:28 PM

To: 'Chanda.Moseley@aventis.com'

Subject: NDA 21-629 color coding comments

Dear Chanda:

I am forwarding the following requests from the chemist regarding the color coding:

1. _____
2. _____
3. _____
4. _____
5. _____

Please let me know when we could expect your response.

Regards,

Julie

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

/s/

Julie Rhee
4/7/04 05:26:48 PM

Rhee, H Julie

From: Moore, Stephen K
Sent: Wednesday, April 07, 2004 5:25 PM
To: Rhee, H Julie
Cc: Ysern, Xavier J; Fraser, Blair; Ripper, Leah W; Moore, Stephen K; Duffy, Eric P; Brown, Janice
Subject: RE: NDA 21-629 / Apidra Revised Labeling
Sensitivity: Confidential

Julie,

Please send the following comments to Aventis regarding insulin color coding:

Steve

1.

2.

3.

4.

5.

-----Original Message-----

From: Moore, Stephen K
Sent: Wednesday, April 07, 2004 4:30 PM
To: Duffy, Eric P; Rhee, H Julie
Cc: Ysern, Xavier J; Fraser, Blair; Ripper, Leah W
Subject: RE: NDA 21-629 / Apidra Revised Labeling
Sensitivity: Confidential

Eric,

Julie,

Stephen

-----Original Message-----

From: Duffy, Eric P
Sent: Wednesday, April 07, 2004 10:07 AM
To: Moore, Stephen K
Subject: FW: NDA 21-629 / Apidra Revised Labeling
Sensitivity: Confidential

Steve -

What is the status of the final review?

- Eric

-----Original Message-----

From: Ripper, Leah W
Sent: Tuesday, April 06, 2004 5:33 PM
To: Rhee, H Julie
Cc: Duffy, Eric P
Subject: RE: NDA 21-629 / Apidra Revised Labeling
Sensitivity: Confidential

Julie, I didn't see revised carton and Container labels in this submission. what is their status?

Lee

Lee W. Ripper
Associate Director for Regulatory Affairs
Office of Drug Evaluation II
Office of New Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Phone: 301-827-5921
Fax: 301-480-6644
Email: leah.ripper@fda.hhs.gov

-----Original Message-----

From: Rhee, H Julie
Sent: Tuesday, April 06, 2004 5:17 PM
To: Meyer, Robert J; Orloff, David G; Gabry, K. Eddie; Moore, Stephen K; Ysern, Xavier J; El Hage, Jeri D; Rhee, Hee M (Herman); Ahn, Hae Young; Wei, Xiaoxiong; Sahlroot, Jon T; Pian, Lee Ping; Hu, Elaine J; Ripper, Leah W
Subject: FW: NDA 21-629 / Apidra Revised Labeling
Importance: High
Sensitivity: Confidential

This is Aventis' response to our revised labeling. An internal labeling to discuss this labeling has been scheduled next Monday April 12.

Thanks,

4/7/2004

Julie

-----Original Message-----

From: Eric.Floyd@aventis.com [mailto:Eric.Floyd@aventis.com]

Sent: Tuesday, April 06, 2004 5:09 PM

To: rheej@cdcr.fda.gov

Cc: Chanda.Moseley@aventis.com

Subject: NDA 21-629 / Apidra Revised Labeling

Importance: High

Sensitivity: Confidential

Julie, I am providing this on behalf of Dr. Chanda Moseley. Her computer is down.

Dear Julie,

As mentioned in an earlier email, I want to inform you that the Aventis responses to the FDA's revisions of the draft labeling for Apidra have been submitted to the FDA today. This submission should be received tomorrow. I am also sending to you now by email the 3 labeling documents, as well as the cover letter and FDA form 356h, that were included in the submission.

Also, in this email I have included, for your convenience, the running text mock-up (the proposed labeling text with revision marks).

Please confirm receipt of these emailed documents. Also, do not hesitate to contact me if you have any questions.

Sincerely,

Chanda

(908) 231-4222

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

/s/

Julie Rhee
4/7/04 05:29:14 PM
CSO

-----Original Message-----

From: Rhee, H Julie

Sent: Tuesday, April 06, 2004 3:38 PM

To: Rhee, H Julie

Subject: FW: NDA 21-629 Apidra

The following is the attachment that was attached to my October 17, 2003, e-mail to Mr. Michael Lutz at Aventis. However, I was not able to copy/paste the content of the attachment in the 10/17/03 e-mail because it did not have a cursor. Therefore, I have forwarded the 10/17/03 e-mail to myself today (4/5/04) in an attempt to copy/paste the following additional clinical information request that was sent to Mr. Michael Lutz on 0/17/03 as an e-mail attachment.

The original attachment was formatted in Landscape but because I could not use Landscape format in the e-mail, I've changed the font size to 8 on the first table. I also changed from Landscape to Portrait.

NDA 21629 Apidra (insulin glulisine [rDNA origin] for injection)

We are reviewing the Clinical section of your June 18, 2003, submission and have the following comments and information requests. Please provide requested data in both a pdf and MS Word document and submit them to the Electronic Document Room.

Treatment-emergent Adverse Cardiac Events, Cardiovascular History, History of Cardiac Events, and Additional Information Regarding Hypoglycemia and Possible Relation to Emergent Cardiac Events

1. Please submit data of all patients with treatment emergent cardiac adverse events, by study, in a tabular form. Please provide a separate table for each study. Please submit data for all clinical studies, including Studies 3001, 3002, 3004, 3006, 3005, 3100 and 3012. A shell outline with some data from Study 3001 is indicated below as an example.

The "history of cardiovascular disease" category should include any history of angina, coronary artery disease, myocardial infarction, arrhythmia, or other cardiovascular disease, with dates or patient's age at that time. Please also include any history of hypertension, as well as past or current history of smoking (please quantitate number of cigarettes per day), and lipid profile on entry into study, as well as any antihypertensive and /or antihyperlipidemic medications. Since this category of cardiovascular disease encompasses a lot of information, a separate table may be necessary to include all the cardiovascular-related data for each patient with a treatment emergent cardiac adverse event.

Patient ID	Study Drug	Age/ Sex / Race	Duration of Diabetes Mellitus	History of Coronary Artery Disease	Cardiac Evaluation during study	Categorization as AE/SAE/WD	Description of cardiac treatment emergent adverse event	Time to onset of cardiac TEAE (i.e. # days after study drug or placebo initiation)	#Episodes of Hypoglycemia (list serious and non-serious separately) and time of onset for SAE hypoglycemia	Related to Hypoglycemia	Is TEAE related to drug?
0806/06	glulisine					SAE	coronary artery disease				
0911/11	glulisine					SAE	coronary artery disease				
1202/09	glulisine					SAE	acute myocardial infarction				
1503/02	glulisine					SAE	myocarditis				
1401/05	glulisine					SAE WD	angina pectoris and acute myocardial infarction				

2. Please submit patient profiles and CRFs for all patients with cardiac TEAEs in the different studies, including any additional information regarding the history of cardiac disease in each patient, any cardiac evaluation during the study (e.g., angina, myocardial infarct, arrhythmia, catheterization, angioplasty, stress test, coronary artery bypass graft surgery), time to onset (from baseline drug initiation day) of cardiac TEAE and clinical history of event and outcome.

3. Please submit tables, by study, summarizing the cardiac histories of patients at enrollment.

A sample table shell is outlined below. Please complete for *studies 3001, 3002, 3004, 3006, 3005, 3100 and 3012.

Please define working definition of "cardiac disease."

Please also compare the number of patients on glulisine and comparator - with and without cardiac disease, according to the following three categories (in addition to the list of cardiac treatment emergent adverse effects and episodes of hypoglycemia):

- (a) hypertension or history of hypertension, at baseline;
- (b) current or prior smoking history;

(c) presence of hyperlipidemia, with of presence of LDL > 130 mg/dl, and fasting triglyceride > 180 mg/dl.

Study * [for all studies, separately by study]	Total	# (%) with a History of Cardiac Disease; also indicate % male	# (%) without a History of Cardiac Disease; also indicate % male
#patients screened			
#patients randomized to glulisine			
# patients randomized to comparator (please indicate comparator)			
#patients treated with glulisine with cardiac TEAE			
#patients treated with comparator with cardiac TEAE			
#cardiac TEAE in glulisine-treated group			
#cardiac TEAE in comparator -treated group			
#patients treated with glulisine with adverse event(s) of hypoglycemia (please indicate separately for serious and non-serious adverse events)			
# hypoglycemia SAE (glulisine group)			
#patients treated with comparator with adverse event(s) of hypoglycemia (please indicate separately for serious and non-serious adverse events)			
# hypoglycemia (comparator group)			
Baseline hypertension (treated or untreated) or history of hypertension in			

glulisine group			
Baseline hypertension (treated or untreated) or history of hypertension in comparator group			
Current or prior smoking history in glulisine group			
Current or prior smoking history in comparator group			
Baseline LDL > 130 mg/dl In glulisine group and/or treatment for hyperlipidemia			
Baseline LDL > 130 mg/dl In comparator group and/or treatment for hyperlipidemia			
Baseline fasting triglyceride > 180 mg/dl in glulisine group and/or treatment for hypertriglyceridemia			
Baseline fasting triglyceride > 180 mg/dl in comparator group and/or treatment for hypertriglyceridemia			

-----Original Message-----

From: Rhee, H Julie

Sent: Friday, October 17, 2003 9:16 AM

To: 'Michael.Lutz@aventis.com'

Subject: NDA 21-629 Apidra

Hi Michael,

I am sending this additional clinical information request to you since Dr. Ernoux said she is not sure whether or not she has a secured e-mail account with us. Could you please forward this e-mail to Dr. Ernoux?

Thanks,

Julie

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

/s/

Julie Rhee
4/6/04 03:59:50 PM

Rhee, H Julie

From: Rhee, H Julie

Sent: Wednesday, March 17, 2004 11:50 AM

To: 'Chanda.Moseley@aventis.com'

Subject: NDA 21-629 Apidra CMC additional information request

Dear Chanda:

I am forwarding additional information request letter from Chemistry. Our document room will send you a hard copy of the letter.

If it's possible at all, could you please respond by cob next Tuesday, March 23?

Thank you,

Julie

3/17/2004