

Rhee, H Julie

From: Rhee, H Julie
Sent: Wednesday, March 17, 2004 11:54 AM
To: 'Odile.Ernoux@aventis.com'
Subject: NDA 21-629 Apidra

Dear Dr. Ernoux:

I just sent an e-mail with an attachment to Chanda Moseley requesting additional CMC information request. I've requested your response by cob next Tuesday March 23. Could you please let me know whether or not you can respond by next Tuesday?

Also, have you submitted Form FDA 3542a yet?

Thank you,

Julie

3/17/2004



NDA 21-629

INFORMATION REQUEST LETTER

Aventis Pharmaceuticals, Inc.
Attention: Odile Ernoux, M.D.
Director Regulatory Liaison
200 Crossing Boulevard
Mail Station BX2 306
Bridgewater, NJ 08807-0890

3/17/04

Dear Dr. Ernoux:

Please refer to your June 18, 2003, new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Apidra™ (insulin glulisine [rDNA origin]) injection.

We are reviewing the Chemistry, Manufacturing and Controls section of your submission and have the following comments and information requests. We request a prompt written response in order to continue our evaluation of your NDA.

I. **Drug Substance:**

1. **Manufacturing Process:**

Data to support the process removal of _____ should be provided.

2. **Specifications:**

- a. The bioidentity test for glulisine should not be deleted but instead retained in the drug substance specifications. This is consistent with the USP monograph for human insulin which includes bioidentity testing.
- b. Since the _____ sequence contained within the insulin glulisine fusion protein differs from the _____ sequence of human insulin, it may be immunogenic. Therefore, testing for the precursor form _____ insulin-glulisine should not be deleted but instead retained in the drug substance specifications. This test is referred to in the NDA as _____ on page 35 of S.3.2. If this test is performed as a process control, this information can be added as a footnote on the specification sheet.

3. Stability:

A retest period for the drug substance of 24 months at the recommended storage temperature (-20 °C) was proposed in the NDA. However, since this is a biotechnology-derived protein product and the level of total related impurities is observed to increase during storage, an expiration dating period should be established. The expiration dating period can be extended based on long-term stability data in accordance with your stability protocol.

II. Drug Product:

Insulin Pumps:

In the insulin pump(s) studies the level of *m*-cresol was observed to decrease in concentration at the needle end of the catheter as compared to the concentration in the reservoir. Data should be provided to support that antimicrobial effectiveness is maintained for the lowest observed level of *m*-cresol in the insulin formulation at the needle end of the catheter tubing.

Although not deficiencies, we have the following requests:

1. _____ (code name) should be changed to _____
_____ on the drug substance specification sheet.
2. _____ HMR 1964 (code name) should be changed to _____
_____ on the drug substance specification sheet.

If you have any questions, call Julie Rhee, Regulatory Project Manager, at (301) 827-6424.

Sincerely,

Stephen K. Moore, Ph.D.
Chemistry Team Leader I for the
Division of Metabolic
and Endocrine Drug Products, HFD-510
DNDC II, Office of New Drug Chemistry
Center for Drug Evaluation and Research

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/s/

Stephen Moore
3/17/04 11:36:45 AM

Rhee, H Julie

From: Moore, Stephen K
Sent: Tuesday, March 16, 2004 5:14 PM
To: Rhee, H Julie
Cc: Ysern, Xavier J
Subject: FW: 21-629 deficiencies
Julie,

Please see attached file for IR letter. Thanks.

Steve and Xavier
-----Original Message-----

From: Ysern, Xavier J
Sent: Tuesday, March 16, 2004 5:06 PM
To: Moore, Stephen K
Subject: 21-629 deficiencies

List of Deficiencies to be Communicated

Drug Substance:

Manufacturing Process:

(1) Data to support the process removal of _____ should be provided.

Specifications:

(2) The _____ sequence coded in the glulisine fusion protein differs from _____ sequence of human insulin, therefore may be immunogenic. Testing for the precursor form _____ should be retained in the drug substance specifications. This test is referred to in your application as _____ on page 35 of S.3.2. If this test is performed as a process control, this can be included as a footnote to the specification sheet.

(3) Consistent with USP monograph for human insulin that includes bioidentity testing, the bioidentity test for glulisine should be retained as part of the drug substance specifications.

Stability:

(4) A retest period for the drug substance of 24 month at the recommended temperature condition, -20 °C, was proposed in your application. However, since this is a biotechnology-derived protein product and the level of total related impurities is observed to increase during storage, an expiration dating period should be established. The expiration dating period can be extended based on long-term stability data in accordance with your stability protocol.

Drug Product:

Insulin Pumps

(5) In the insulin pumps studies the level of *m*-cresol was observed to decrease in concentration at the needle end of the catheter as compared to the concentration on the reservoir. Data should be provided to support that antimicrobial effectiveness is maintained for the maximal percentage drop in the level of *m*-cresol at the needle end of the catheter tubing of the insulin pump.

Although not deficiencies, the following are requested:

- (1) _____ (code name) should be changed to _____ on the drug substance specification sheet.
- (2) _____ (code name) should be changed to _____ on the drug substance specification sheet.



MEMORANDUM

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

DATE: March 11, 2004

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

FROM: Office of Drug Safety

Mark Avigan, M.D., Director
Division of Drug Risk Evaluation, HFD-430

Jerry Phillips, RPh. Acting Director,
Division of Medication Error and Technical Support, HFD-420

Gerald DalPan, M.D., Director
Division of Surveillance, Research and Communication Support, HFD-410

DRUG: Apidra (insulin glulisine)

NDA #: 21-629

SUBJECT: ODS Review of Proposed Risk Management Plan (RMP)

PID #: D030541

Overall, the Apidra (insulin glulisine) Risk Management Plan, as submitted on June 18, 2003 does not appear to differ substantially from a typical new product labeling and routine passive post-marketing safety surveillance.

The Office of Drug Safety has reviewed the submitted RMP and has determined that it does not identify a specific safety concern for which a RMP to minimize risk would be normally associated. Thus we are deferring any comment on the submitted plan.

Mark Avigan, M.D., Director
Division of Drug Risk Evaluation, HFD-430

Jerry Phillips, RPh. Acting Director
Division of Medication Error and Technical Support, HFD-420

Gerald DalPan, M.D., Director
Division of Surveillance, Research and Communication Support, HFD-410

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/s/

Mary Dempsey
3/11/04 05:11:12 PM
DRUG SAFETY OFFICE REVIEWER

Mark Avigan
3/11/04 05:30:54 PM
DRUG SAFETY OFFICE REVIEWER

Jerry Phillips
3/12/04 07:56:50 AM
DRUG SAFETY OFFICE REVIEWER

Gerald DalPan
3/12/04 08:10:12 AM
MEDICAL OFFICER

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

(b4)

Memo

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

From: Felicia Duffy, RN, BSN
Safety Evaluator, Division of Medication Errors and Technical Support
Office of Drug Safety; HFD-420

Through: Alina Mahmud, R.Ph.
Team Leader, Division of Medication Errors and Technical Support
Office of Drug Safety; HFD-420

Carol Holquist, R.Ph.
Deputy Director, Division of Medication Errors and Technical Support
Office of Drug Safety; HFD-420

Jerry Phillips, R.Ph.
Associate Director, Division of Medication Errors and Technical Support
Office of Drug Safety; HFD-420

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

Date: March 3, 2004

Re: ODS Consult 03-0180-3; Apidra (Insulin Glulisine [recombinant DNA origin] Injection);
NDA 21-629.

This memorandum is in response to a February 6, 2004 request from your Division for a re-review of the proprietary name, Apidra. The proposed proprietary name, Apidra, was found acceptable by DMETS in a review dated August 5, 2003 (ODS Consult # 01-0180). Please refer to ODS Consult #01-0180, Section III, for DMETS comments on the carton and container labeling. DMETS comments on the patient package insert were made in a joint review from DSCRS dated January 15, 2003.

Since DMETS last review, the Agency received a General Correspondence letter dated December 2, 2003, from _____ states that the proposed name "Apidra" is the word "Rapid" with a transposition of the letters: apid(Ra). DMETS acknowledges the sponsors comments, however the transposition is not intuitive, especially since Apidra contains more letters than that contained in the word "Rapid". Additionally, these concerns were forwarded to the Division of Drug Marketing, Advertising, and Communications (DDMAC) for their comment on this issue. Following review of this additional information, DDMAC maintains their position that there are no promotional concerns with the proposed

proprietary name, Apidra. _____ brought this issue to the attention of the Agency because they were denied the use of the proprietary name _____ because it contained the word "Rapid". However, DMETS did not review the proprietary name _____ and therefore cannot comment further on this decision.

From a safety perspective, DMETS has not identified any additional proprietary or established names that have the potential for confusion with Apidra since we conducted our review on August, 5 2003 (ODS Consult # 01-0180), that would render the name objectionable. Therefore, we have no objections to the use of this proprietary name.

We consider this a final review. However, if the approval of the NDA is delayed beyond 90 days from the date of this review, the name must be re-evaluated. A re-review of the name before NDA approval will rule out any objections based upon approvals of other proprietary/established names from this date forward.

If you have any questions or need clarification, please contact the medication errors project manager, Sammie Beam at 301-827-3242.

**APPEARS THIS WAY
ON ORIGINAL**

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/s/

Felicia Duffy
3/18/04 10:16:48 AM
DRUG SAFETY OFFICE REVIEWER

Alina Mahmud
3/18/04 10:42:37 AM
DRUG SAFETY OFFICE REVIEWER

Carol Holquist
3/18/04 12:54:51 PM
DRUG SAFETY OFFICE REVIEWER

Jerry Phillips
3/19/04 07:33:36 AM
DRUG SAFETY OFFICE REVIEWER



February 20, 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)
Final response to February 4, 2004 request
for additional clinical information: Question 1

Dear Dr. Orloff:

Reference is made to the above-mentioned New Drug Application (NDA) for APIDRA™ (HMR 1964 – insulin glulisine), which was submitted to the Agency on June 18, 2003.

The purpose of this February 20, 2004 correspondence is to submit responses to Question 1 of your February 4, 2004 request for additional clinical information regarding APIDRA™. Responses to Questions 6, 9 and 10 were submitted to the Agency on February 12, 2004, and responses to Questions 2, 3, 4, 5, 7, and 8 were submitted on February 17, 2004.

This submission is fully electronic and provided on the enclosed CD (approximately 150KB). 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 60218u, February 18, 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,

A handwritten signature in black ink, appearing to read "Odile Ernoux", written over a horizontal line.

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



February 17, 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)
Response to February 4, 2004 request
for additional clinical information: Questions 2, 3, 4, 5, 7, and 8

Dear Dr. Orloff:

Reference is made to the above-mentioned New Drug Application (NDA) for APIDRA™ (HMR 1964 – insulin glulisine), which was submitted to the Agency on June 18, 2003.

The purpose of this February 17, 2004 correspondence is to submit responses to Questions 2, 3, 4, 5, 7, and 8 of your February 4, 2004 request for additional clinical information regarding APIDRA™. Responses to Questions 6, 9 and 10 were submitted to the Agency on February 12, 2004. A response to Question 1 will be submitted on February 19, 2004.

During the preparation of responses to questions relating to severe hypoglycemia, a difference was noted in the number of episodes identified by application of a) the definition of severe hypoglycemia in the clinical study protocols and b) the implementation used by the software programming to classify a hypoglycemic event as "severe."

Although the clinical study protocols defined "severe hypoglycemia" as an episode requiring assistance AND having either a blood glucose <36 mg/dl or prompt recovery following administration of oral carbohydrate, IV glucose or glucagon injection, the programming erroneously classified hypoglycemic episodes as "severe" in the Phase III studies using only one element of the protocol definition, the "required assistance" criterion.

After careful review, however, both definitions identified essentially the same number of episodes, with the programming definition identifying 9 more of these safety events. The attached table shows that the "programming definition" identified 343 episodes (208 + 135 for HMR1964 and comparator, respectively) compared with 334 episodes (206 + 128 for HMR1964 and comparator, respectively) by the narrower definition in the clinical study protocols.

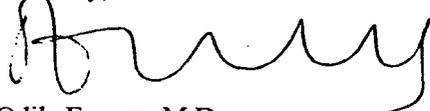
The relevant data for the 9 discrepant episodes is provided. In 8 of these cases, the investigator did not provide data for 'blood glucose <36 mg/dl' or 'prompt recovery following administration of oral carbohydrate, IV glucose or glucagon injection'. Eight of the nine cases were reported by the investigator as "serious criteria fulfilled."

Despite the differently applied criteria, the number of episodes is substantially the same with 97% concordance. For this reason and in order to maintain consistency in reporting data from the glulisine program, the attached responses to questions by Medical Officer Zawadski regarding "severe hypoglycemia" use the programming definition.

This submission is fully electronic and provided on the enclosed CD (approximately 1 MB). 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 60217e, February 17, 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,

A handwritten signature in black ink, appearing to read "Odile Ernoux". The signature is fluid and cursive, with a long horizontal line extending from the end of the name.

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

ATTACHMENT

Number -- subjects/episodes of severe hypoglycemia, by programming and study report definition (missing data are treated as criteria not confi. d.)
Treatment period

Type	Study	Programming definition				Report definition				Difference: Prog. def. - Report def.			
		HMR1964		Comparator		HMR1964		Comparator		HMR1964		Comparator	
		Number of subjects	Number of episodes	Number of subjects	Number of episodes	Number of subjects	Number of episodes	Number of subjects	Number of episodes	Number of subjects	Number of episodes	Number of subjects	Number of episodes
Nocturnal severe	3001	21	25	10	15	21	25	9	14	0	0	1	1
	3002	8	10	6	6	7	9	5	5	1	1	1	1
	3004	37	49	13	15	36	48	11	13	1	1	2	2
	3005	3	3	5	6	3	3	5	6	0	0	0	0
	3006	2	2	0	0	2	2	0	0	0	0	0	0
	3011 (extension)	10	11	8	8	10	11	8	8	0	0	0	0
	3012 (extension)	2	3	1	1	2	3	1	1	0	0	0	0
	Overall	77	103	43	51	75	101	39	47	2	2	4	4
Non-nocturnal severe	3001	23	36	21	32	23	36	21	32	0	0	0	0
	3002	12	12	6	6	12	12	6	6	0	0	0	0
	3004	16	27	16	24	16	27	16	22	0	0	0	2
	3005	3	6	9	10	3	6	8	9	0	0	1	1
	3006	0	0	2	2	0	0	2	2	0	0	0	0
	3011 (extension)	16	18	5	10	16	18	5	10	0	0	0	0
	3012 (extension)	5	6	0	0	5	6	0	0	0	0	0	0
	Overall	67	105	58	84	67	105	57	81	0	0	1	3
All Severe	3001	38	61	29	47	38	61	28	46	0	0	1	1
	3002	17	22	12	12	17	21	11	11	0	1	1	1
	3004	49	76	28	39	48	75	26	35	1	1	2	4
	3005	6	9	14	16	6	9	13	15	0	0	1	1
	3006	2	2	2	2	2	2	2	2	0	0	0	0
	3011 (extension)	22	29	10	18	22	29	10	18	0	0	0	0
	3012 (extension)	6	9	1	1	6	9	1	1	0	0	0	0
	Overall	125	208	95	135	124	206	90	128	1	2	5	7

Note: 'Pre-meal HMR1964', and 'Post-meal HMR1964' groups are combined in presenting study 3004 results.
Treatment group 'Comparator' include 'Regular Insulin' for studies 3002, 3012, 3004 and 3005, 'Lispro' for study 3001 and 3011, and 'Aspart' for study 3006.

List of hypoglycemia episodes which required assistance but with neither counter-measurements nor blood glucose value < 36 mg/dL or with severity not determinable due to missing data -- (Treatment period)

Study/ site/ subject	S e Age x Treatment	Severe hypoglycemia episode								Last fast-acting insulin injection			Last basal insulin injection		
		Start date	Start day	Start time (HH:MM)	Assist- ance	Counter- measure- ments	Blood glucose (mg/dL)	Serious?	Symptoms	Date	Time (HH:MM)	Dose (IU)	Date	Time (HH:MM)	Dose (IU)
3001/0806/12	31 F Comparator	09MAR02	96	-*	Yes	None	-	Yes	UNCONSCIOUSNESS.	08MAR02	19:00	14	08MAR02	19:00	5
3002/0114/01	61 M HMR1964	16NOV01	40	1:30*	Yes	None	-	No	SWEATING; IRRITABLE; LACK OF BALANCE.	-	-	-	-	-	-
3002/0302/05	60 M Comparator	19JUN02	120	3:05*	Yes	None	339	Yes	SWEATING; NAUSEA; CONFUSION.	-	17:00	14	-	17:00	38
3004/4116/22	31 M HMR1964	09MAR02	87	1:45*	Yes	-	67	Yes	SWEATING; HUNGER; WEAKNESS/TIREDNE SS; DIZZINESS; LIGHTEADED; HEADACHE.	-	19:00	15	-	23:00	33
3004/4116/42	37 M Comparator	19MAR02	68	1:30*	Yes	-	98	Yes	SWEATING; TREMOR; CONVULSIONS; UNCONSCIOUSNESS.	-	19:00	13	-	21:50	75
3004/4126/02	42 M Comparator	27DEC01	17	18:45	Yes	-	57	Yes	UNCONSCIOUSNESS; INCOHERENT; DECREASED VISION.	-	17:45	7	-	22:30	28
3004/4145/21	39 M Comparator	07JUN02	36	-	Yes	-	-	Yes	UNCONSCIOUSNESS.	-	-	-	-	-	-
3004/4201/14	23 F Comparator	12MAY02	49	11:00*	Yes	-	-	Yes	CONVULSIONS; UNCONSCIOUSNESS.	-	8:30	14	-	23:00	28
3005/0452/14	57 M Comparator	11MAR03	181	-	Yes	None	-	Yes	UNCONSCIOUSNESS.	-	-	-	-	-	-

Note: '*' : Recorded as nocturnal episode.

'Pre-meal HMR1964', and 'Post-meal HMR1964' groups are combined in presenting study 3004 results.

Treatment group 'Comparator' include 'Regular Insulin' for studies 3002, 3012, 3004 and 3005, 'Lispro' for study 3001 and 3011, and 'Aspart' for study 3006.

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/s/

Stephen Moore
3/17/04 11:36:45 AM



February 12, 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)
Response to February 4, 2004 request
for additional clinical information: Questions 6, 9 and 10**

Dear Dr. Orloff:

Reference is made to the above-mentioned New Drug Application (NDA) for APIDRA™ (HMR 1964 – insulin glulisine), which was submitted to the Agency on June 18, 2003.

The purpose of this February 12, 2004 correspondence is to submit responses to Questions 6, 9, and 10 of your February 4, 2004 request for additional clinical information regarding APIDRA™. Responses to Questions 2, 3, 4, 5, 7, 8a, and 8b will be submitted to the Agency on February 17, 2004, and a response to Question 1 will be submitted on February 19, 2004.

This submission is fully electronic and provided on the enclosed CD (approximately 500 KB). 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 60209h, February 9, 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,

A handwritten signature in cursive script that reads "Odile Ernoux".

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



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

FEB 12 2004

Dear Dr. _____

Between December 16 and 18, 2003, Mr. Michael R. Goga, representing the Food and Drug Administration (FDA), conducted an investigation and met with you to review your conduct of a clinical investigation (protocol #HMR1964A/3004 entitled: "12-Week, Multinational, Multicenter, Controlled, Open, 1:1:1 Randomized, Parallel Clinical Trial to Assess Noninferiority Between Pre- and Post-Meal Administration of HMR1964 and Pre-Meal Regular Human Insulin in Subjects with Type 1 Diabetes Mellitus Receiving Insulin Glargine as the Basal Insulin Therapy") of the investigational drug Apidra™ (insulin glulisine [rDNA origin]), performed for Aventis Pharmaceuticals, Inc. This inspection is a part of FDA's Bioresearch Monitoring Program, which includes inspections designed to evaluate the conduct of research and to ensure that the rights, safety, and welfare of the human subjects of the study have been protected.

From our evaluation of the establishment inspection report and the documents submitted with that report, we conclude that you adhered to the applicable statutory requirements and FDA regulations governing the conduct of clinical investigations and the protection of human subjects.

We appreciate the cooperation shown Investigator Goga 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,

/s/

Khin Maung U, M.D.
Branch Chief
Good Clinical Practice Branch I, HFD-46
Division of Scientific Investigations
Office of Medical Policy
Center for Drug Evaluation and Research
7520 Standish Place, Room 125
Rockville, MD 20855

CFN/FEI: 3004144795

Field Classification: NAI

Headquarters Classification:

1)NAI

2)VAI- no response required

3)VAI- response requested

4)OAI

cc:

HFA-224

HFD-510 Doc.Rm. NDA#21-629

HFD-510 Review Div.Dir./Orloff

HFD-510 MO/Zawadzki

HFD-510 PM/Rhee

HFD-46/47c/t/s/ GCP File #11118

HFD-46/47 GCP Reviewer/Slavin

HFR-SW240 DIB/Miller

HFR-SW2520 Bimo Monitor/Thompson

HFR-SW240 Field Investigator/Goga

GCF-1 Seth Ray

r/d: AS: 2/10/04

reviewed:KMU:2/10/04

f/t:ml/sg:2/11/04

Reviewer Note to Rev. Div. M.O.

This was a routine PDUFA inspection conducted in support of NDA 21-629, Apidra™ (insulin glulisine). This was Dr. — initial inspection. Dr. — screened 43 subjects and randomized 39 subjects. All thirty-nine subjects completed the study. The inspection encompassed a review of 33 subjects' consent forms. All subjects signed consent forms prior to the initiation of study procedures. The following subjects' records were reviewed for GHb values: subject #'s 001, 002, 003, 007, 017, 022, 027, 034, and 042. Per protocol, the sites were blinded to GHb values at visit 6 (baseline) and visit 10 (week 8). Therefore, the only GHb values available at the site to be verified were the screening (visit 1) and endpoint (visit 11) values. At the completion of the inspection, the FDA investigator discussed 4 minor deficiencies with Dr. — subject 034 recorded an episode of hypoglycemia in his/her diary on 1/13/02 at 11:43am; subject did not record what actions were taken to relieve the symptoms of hypoglycemia, and if he/she needed assistance from another person; the CRF for this episode documents that the subject required no assistance from another person, and that the hypoglycemia was relieved with an oral carbohydrate, subject 0020 did not sign the 11/27/01 version of the consent form until 2/25/02, subject 001 had 2 screening GHb lab reports in his/her file, and there were numerous instances in which subjects did not perform the 7-point blood glucose profiles that were required by the protocol. A Form FDA 483 was not issued. The inspection is classified as NAI. Data from this site are acceptable in support of NDA 21-629.

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/s/

Khin U

2/23/04 08:20:06 AM

Aventis Pharmaceuticals

February 10, 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

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FDR/CDER

N-000-BM

**NDA 21-629: APIDRA™
HMR 1964 – Insulin glulisine (rDNA human insulin analog)
Clinical Study Report for Study 3005**

Dear Dr. Orloff:

Reference is made to the above-mentioned New Drug Application (NDA) for APIDRA™ (HMR 1964 – insulin glulisine), which was submitted to the Agency on June 18, 2003.

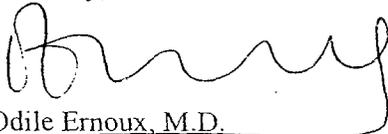
The purpose of this February 10, 2004 correspondence is to submit the final clinical study report for the Phase III study 3005. Key safety and efficacy tables (176) for this study were previously submitted on November 4, 2003 as part of the 120-day safety update for the APIDRA™ NDA. Also, in this safety update, final datasets [including SAS transport files (Xpt files)], narratives and CRFs for study 3005 were also included. In the final study report, 3 of the previously 176 submitted tables have been updated. Details on these updates are attached.

In accordance to 21 CFR 314.60, this submission constitutes a minor amendment to NDA 21-629.

This submission is fully electronic and provided on the enclosed CD (approximately 40 MB). 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 60204d, February 4, 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 me 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

In the final 3005 Clinical Study Report, the following end-of-text tables have been updated.

1. Two tables were not further referenced in the body of the text and therefore not included in the final CSR end of text tables:

a) Interim Table T-75 (1do0101t.lst): Short-acting insulin injection site - PP population

b) Interim Table T-76 (1do0102t.lst): Average number of daily short-acting insulin injections - PP population

2. CSR Table T-38, Interim Table T-37 (1ef0001t.lst): Numbers of subjects in efficacy analyses - ITT and PP populations

Three new rows were added:

PG prior to first meal

PG 1 hour after test meal

PG 2 hours after test meal

3. CSR Table T-168, Interim Table T-161 (1ql0009t.lst): Treatment satisfaction (DTSQ, change version): ANCOVA results - ITT population

For this quality of life analysis table, 'Treatment Satisfaction score, Endpoint' in Treatment of HMR1964: Updated N=197 from N=198.

4) CSR Table T-159, Interim Table T-169 (1ql0017t.lst): Treatment Satisfaction (DTSQ, status version): Analysis of change from start of screening/run-in phase (visit 2; week -4) - ITT population

For this quality of life analysis table, 'Treatment Satisfaction score run in /screening [a]' in Treatment of HMR1964: Updated N=282 from N=281.

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

Form Approved: OMB No. 0910-0338
Expiration Date: August 31, 2005
See OMB Statement on page 2.

**APPLICATION TO MARKET A NEW DRUG, BIOLOGIC,
OR AN ANTIBIOTIC DRUG FOR HUMAN USE**
(Title 21, Code of Federal Regulations, Parts 314 & 601)

FOR FDA USE ONLY

APPLICATION NUMBER

APPLICANT INFORMATION

NAME OF APPLICANT Aventis Pharmaceuticals, Inc.	DATE OF SUBMISSION 2/10/04
TELEPHONE NO. (Include Area Code) (908) 231-3536	FACSIMILE (FAX) Number (Include Area Code) (908) 304-6318
APPLICANT ADDRESS (Number, Street, City, State, Country, ZIP Code or Mail Code, and U.S. License number if previously issued): 200 Crossing Boulevard PO Box 6890 Bridgewater, NJ 08807-0890	AUTHORIZED U.S. AGENT NAME & ADDRESS (Number, Street, City, State, ZIP Code, telephone & FAX number) IF APPLICABLE RECEIVED FEB 11 2004 CDR/CDER

PRODUCT DESCRIPTION

NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER, OR BIOLOGICS LICENSE APPLICATION NUMBER (If previously issued) NDA 21-629		
ESTABLISHED NAME (e.g., Proper name, USP/USAN name) Insulin glulisine	PROPRIETARY NAME (trade name) IF ANY APIDRA™	
CHEMICAL/BIOCHEMICAL/BLOOD PRODUCT NAME (If any) 3B Lys-29B-Glu-human insulin	CODE NAME (If any) HMR 1964	
DOSAGE FORM: Injection	STRENGTHS: 100 IU/mL	ROUTE OF ADMINISTRATION: Subcutaneous
(PROPOSED) INDICATION(S) FOR USE: For treatment of adult patients with diabetes mellitus for the control of hyperglycemia		

APPLICATION TYPE

APPLICATION TYPE (check one)		
<input checked="" type="checkbox"/> NEW DRUG APPLICATION (21 CFR 314.50)	<input type="checkbox"/> ABBREVIATED NEW DRUG APPLICATION (ANDA, 21 CFR 314.94)	
<input type="checkbox"/> BIOLOGICS LICENSE APPLICATION (21 CFR Part 601)		
IF AN NDA, IDENTIFY THE APPROPRIATE TYPE	<input checked="" type="checkbox"/> 505 (b)(1)	<input type="checkbox"/> 505 (b)(2)
IF AN ANDA, OR 505(b)(2), 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)		
<input type="checkbox"/> ORIGINAL APPLICATION	<input type="checkbox"/> AMENDMENT TO PENDING APPLICATION	<input type="checkbox"/> RESUBMISSION
<input type="checkbox"/> PRESUBMISSION	<input type="checkbox"/> ANNUAL REPORT	<input type="checkbox"/> ESTABLISHMENT DESCRIPTION SUPPLEMENT
<input type="checkbox"/> LABELING SUPPLEMENT	<input type="checkbox"/> CHEMISTRY MANUFACTURING AND CONTROLS SUPPLEMENT	<input checked="" type="checkbox"/> OTHER
IF A SUBMISSION OF PARTIAL APPLICATION, PROVIDE LETTER DATE OF AGREEMENT TO PARTIAL SUBMISSION: _____		
IF A SUPPLEMENT, IDENTIFY THE APPROPRIATE CATEGORY		
<input type="checkbox"/> CBE	<input type="checkbox"/> CBE-30	<input type="checkbox"/> Prior Approval (PA)

REASON FOR SUBMISSION

REASON FOR SUBMISSION Clinical study report for study 3005 for APIDRA™ NDA		
PROPOSED MARKETING STATUS (check one)		
<input checked="" type="checkbox"/> PRESCRIPTION PRODUCT (Rx)	<input type="checkbox"/> OVER THE COUNTER PRODUCT (OTC)	
NUMBER OF VOLUMES SUBMITTED	THIS APPLICATION IS	
NA	<input type="checkbox"/> PAPER	<input type="checkbox"/> PAPER AND ELECTRONIC
		<input checked="" type="checkbox"/> ELECTRONIC

ESTABLISHMENT INFORMATION (Full establishment information should be provided in the body of the Application.)

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.

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

This application contains the following items: (Check all that apply)

- 1. Index
- 2. Labeling (check one) Draft Labeling Final Printed Labeling
- 3. Summary (21 CFR 314.50 (c))
- 4. Chemistry section
 - A. Chemistry, manufacturing, and controls information (e.g., 21 CFR 314.50(d)(1); 21 CFR 601.2)
 - B. Samples (21 CFR 314.50 (e)(1); 21 CFR 601.2 (a)) (Submit only upon FDA's request)
 - C. Methods validation package (e.g., 21 CFR 314.50(e)(2)(i); 21 CFR 601.2)
- 5. Nonclinical pharmacology and toxicology section (e.g., 21 CFR 314.50(d)(2); 21 CFR 601.2)
- 6. Human pharmacokinetics and bioavailability section (e.g., 21 CFR 314.50(d)(3); 21 CFR 601.2)
- 7. Clinical Microbiology (e.g., 21 CFR 314.50(d)(4))
- 8. Clinical data section (e.g., 21 CFR 314.50(d)(5); 21 CFR 601.2)
- 9. Safety update report (e.g., 21 CFR 314.50(d)(5)(vi)(b); 21 CFR 601.2)
- 10. Statistical section (e.g., 21 CFR 314.50(d)(6); 21 CFR 601.2)
- 11. Case report tabulations (e.g., 21 CFR 314.50(f)(1); 21 CFR 601.2)
- 12. Case report forms (e.g., 21 CFR 314.50 (f)(2); 21 CFR 601.2)
- 13. Patent information on any patent which claims the drug (21 U.S.C. 355(b) or (c))
- 14. A patent certification with respect to any patent which claims the drug (21 U.S.C. 355 (b)(2) or (j)(2)(A))
- 15. Establishment description (21 CFR Part 600, if applicable)
- 16. Debarment certification (FD&C Act 306 (k)(1))
- 17. Field copy certification (21 CFR 314.50 (l)(3))
- 18. User Fee Cover Sheet (Form FDA 3397)
- 19. Financial Information (21 CFR Part 54)
- 20. OTHER (Specify)

CERTIFICATION

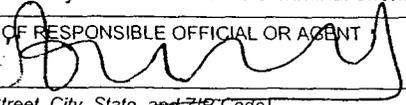
I agree to update this application with new safety information about the product that may reasonably affect the statement of contraindications, warnings, precautions, or adverse reactions in the draft labeling. I agree to submit safety update reports as provided for by regulation or as requested by FDA. If this application is approved, I agree to comply with all applicable laws and regulations that apply to approved applications, including, but not limited to the following:

1. Good manufacturing practice regulations in 21 CFR Parts 210, 211 or applicable regulations, Parts 606, and/or 820.
2. Biological establishment standards in 21 CFR Part 600.
3. Labeling regulations in 21 CFR Parts 201, 606, 610, 660, and/or 809.
4. In the case of a prescription drug or biological product, prescription drug advertising regulations in 21 CFR Part 202.
5. Regulations on making changes in application in FD&C Act Section 506A, 21 CFR 314.71, 314.72, 314.97, 314.99, and 601.12.
6. Regulations on Reports in 21 CFR 314.80, 314.81, 600.80, and 600.81.
7. Local, state and Federal environmental impact laws.

If this application applies to a drug product that FDA has proposed for scheduling under the Controlled Substances Act, I agree not to market the product until the Drug Enforcement Administration makes a final scheduling decision.

The data and information in this submission have been reviewed and, to the best of my knowledge are certified to be true and accurate.

Warning: A willfully false statement is a criminal offense, U.S. Code, title 18, section 1001.

SIGNATURE OF RESPONSIBLE OFFICIAL OR AGENT 	TYPED NAME AND TITLE Odile Ernoux, M.D., U.S. Regulatory Liaison	DATE: Feb 10, 2004
ADDRESS (Street, City, State, and ZIP Code) Aventis Pharmaceuticals, Inc.; 200 Crossing Boulevard, PO Box 6890; Bridgewater, NJ 08807-0890		Telephone Number (908) 231-3536

Public reporting burden for this collection of information is estimated to average 24 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:

Department of Health and Human Services
and Drug Administration
OJER, HFD-99
1401 Rockville Pike
Rockville, MD 20852-1448

Food and Drug Administration
CBER, HFM-94
12420 Parklawn Dr., Room 3046
Rockville, MD 20852

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.

RECEIVED ORIGINAL
FEB 09 2004
CDR/CDER



February 6, 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

RECEIVED
FEB 10 2004
FDR/CDER

N-000-EM

NDA 21-629: APIDRA™
HMR 1964 – Insulin glulisine (rDNA human insulin analog)
Clinical study 3004-hypomeg 1 xpt

ORIG AMENDMENT
2/17/04

Dear Dr. Orloff:

Reference is made to the above-mentioned New Drug Application (NDA) for APIDRA™ (HMR 1964 – insulin glulisine), which was submitted to the Agency on June 18, 2003.

The purpose of this February 6, 2004 correspondence is to submit the xpt file for hypomeg 1 (study 3004) as requested. This file is identical to the one emailed to Lee Ping Pian on February 6th, 2004.

This submission is fully electronic and provided on the enclosed CD (approximately 50 MB). 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 60204d, February 4, 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

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

Form Approved: OMB No. 0910-0338
Expiration Date: August 31, 2005
See OMB Statement on page 2.

**APPLICATION TO MARKET A NEW DRUG, BIOLOGIC,
OR AN ANTIBIOTIC DRUG FOR HUMAN USE**
(Title 21, Code of Federal Regulations, Parts 314 & 601)

FOR FDA USE ONLY

APPLICATION NUMBER

APPLICANT INFORMATION

NAME OF APPLICANT Aventis Pharmaceuticals, Inc.	DATE OF SUBMISSION 2/6/04
TELEPHONE NO. (Include Area Code) (908) 231-3536	FACSIMILE (FAX) Number (Include Area Code) (908) 304-6318
APPLICANT ADDRESS (Number, Street, City, State, Country, ZIP Code or Mail Code, and U.S. License number if previously issued): 200 Crossing Boulevard PO Box 6890 Bridgewater, NJ 08807-0890	AUTHORIZED U.S. AGENT NAME & ADDRESS (Number, Street, City, State, ZIP Code, telephone & FAX number) IF APPLICABLE

RECEIVED
FEB 09 2004
CDR/CDER

PRODUCT DESCRIPTION

NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER, OR BIOLOGICS LICENSE APPLICATION NUMBER (If previously issued) NDA 21-629		
ESTABLISHED NAME (e.g., Proper name, USP/USAN name) Insulin glulisine	PROPRIETARY NAME (trade name) IF ANY APIDRA™	
CHEMICAL/BIOCHEMICAL/BLOOD PRODUCT NAME (If any) 3B Lys-29B-Glu-human insulin	CODE NAME (If any) HMR 1964	
DOSAGE FORM: Injection	STRENGTHS: 100 IU/mL	ROUTE OF ADMINISTRATION: Subcutaneous

(PROPOSED) INDICATION(S) FOR USE:
For treatment of adult patients with diabetes mellitus for the control of hyperglycemia

APPLICATION TYPE

(check one) NEW DRUG APPLICATION (21 CFR 314.50) ABBREVIATED NEW DRUG APPLICATION (ANDA, 21 CFR 314.94)
 BIOLOGICS LICENSE APPLICATION (21 CFR Part 601)

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

IF AN ANDA, OR 505(b)(2), 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 APENDING APPLICATION RESUBMISSION
 PRESUBMISSION ANNUAL REPORT ESTABLISHMENT DESCRIPTION SUPPLEMENT EFFICACY SUPPLEMENT
 LABELING SUPPLEMENT CHEMISTRY MANUFACTURING AND CONTROLS SUPPLEMENT OTHER

IF A SUBMISSION OF PARTIAL APPLICATION, PROVIDE LETTER DATE OF AGREEMENT TO PARTIAL SUBMISSION: _____

IF A SUPPLEMENT, IDENTIFY THE APPROPRIATE CATEGORY CBE CBE-30 Prior Approval (PA)

REASON FOR SUBMISSION
Clinical study 3004 - hypomeg 1 xpt for APIDRA™ NDA

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

NUMBER OF VOLUMES SUBMITTED NA THIS APPLICATION IS PAPER PAPER AND ELECTRONIC ELECTRONIC

ESTABLISHMENT INFORMATION (Full establishment information should be provided in the body of the Application.)
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.

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

This application contains the following items: (Check all that apply)

<input type="checkbox"/>	1. Index
<input type="checkbox"/>	2. Labeling (check one) <input type="checkbox"/> Draft Labeling <input type="checkbox"/> Final Printed Labeling
<input type="checkbox"/>	3. Summary (21 CFR 314.50 (c))
<input type="checkbox"/>	4. Chemistry section
<input type="checkbox"/>	A. Chemistry, manufacturing, and controls information (e.g., 21 CFR 314.50(d)(1); 21 CFR 601.2)
<input type="checkbox"/>	B. Samples (21 CFR 314.50 (e)(1); 21 CFR 601.2 (a)) (Submit only upon FDA's request)
<input type="checkbox"/>	C. Methods validation package (e.g., 21 CFR 314.50(e)(2)(i); 21 CFR 601.2)
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<input type="checkbox"/>	7. Clinical Microbiology (e.g., 21 CFR 314.50(d)(4))
<input type="checkbox"/>	8. Clinical data section (e.g., 21 CFR 314.50(d)(5); 21 CFR 601.2)
<input type="checkbox"/>	9. Safety update report (e.g., 21 CFR 314.50(d)(5)(vi)(b); 21 CFR 601.2)
<input type="checkbox"/>	10. Statistical section (e.g., 21 CFR 314.50(d)(6); 21 CFR 601.2)
<input type="checkbox"/>	11. Case report tabulations (e.g., 21 CFR 314.50(f)(1); 21 CFR 601.2)
<input type="checkbox"/>	12. Case report forms (e.g., 21 CFR 314.50 (f)(2); 21 CFR 601.2)
<input type="checkbox"/>	13. Patent information on any patent which claims the drug (21 U.S.C. 355(b) or (c))
<input type="checkbox"/>	14. A patent certification with respect to any patent which claims the drug (21 U.S.C. 355 (b)(2) or (j)(2)(A))
<input type="checkbox"/>	15. Establishment description (21 CFR Part 600, if applicable)
<input type="checkbox"/>	16. Debarment certification (FD&C Act 306 (k)(1))
<input type="checkbox"/>	17. Field copy certification (21 CFR 314.50 (l)(3))
<input type="checkbox"/>	18. User Fee Cover Sheet (Form FDA 3397)
<input type="checkbox"/>	19. Financial Information (21 CFR Part 54)
<input checked="" type="checkbox"/>	20. OTHER (Specify) Clinical study 3004 - hypomeg l xpt for APIDRA™ NDA

CERTIFICATION

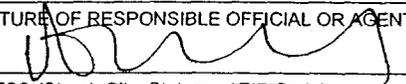
I agree to update this application with new safety information about the product that may reasonably affect the statement of contraindications, warnings, precautions, or adverse reactions in the draft labeling. I agree to submit safety update reports as provided for by regulation or as requested by FDA. If this application is approved, I agree to comply with all applicable laws and regulations that apply to approved applications, including, but not limited to the following:

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3. Labeling regulations in 21 CFR Parts 201, 606, 610, 660, and/or 809.
4. In the case of a prescription drug or biological product, prescription drug advertising regulations in 21 CFR Part 202.
5. Regulations on making changes in application in FD&C Act Section 506A, 21 CFR 314.71, 314.72, 314.97, 314.99, and 601.12.
6. Regulations on Reports in 21 CFR 314.80, 314.81, 600.80, and 600.81.
7. Local, state and Federal environmental impact laws.

If this application applies to a drug product that FDA has proposed for scheduling under the Controlled Substances Act, I agree not to market the product until the Drug Enforcement Administration makes a final scheduling decision.

The data and information in this submission have been reviewed and, to the best of my knowledge are certified to be true and accurate.

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SIGNATURE OF RESPONSIBLE OFFICIAL OR AGENT 	TYPED NAME AND TITLE Odile Ernoux, M.D., U.S. Regulatory Liaison	DATE: Feb 6, 2004
ADDRESS (Street, City, State, and ZIP Code) Aventis Pharmaceuticals, Inc.; 200 Crossing Boulevard, PO Box 6890; Bridgewater, NJ 08807-0890		Telephone Number (908) 231-3536

Public reporting burden for this collection of information is estimated to average 24 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:

Department of Health and Human Services
Food and Drug Administration
CFR, HFD-99
1401 Rockville Pike
Rockville, MD 20852-1448

Food and Drug Administration
CBER, HFM-94
12420 Parklawn Dr., Room 3046
Rockville, MD 20852

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.

RECEIVED
FEB 09 2004
CDR/CDER

ORIGINAL



RECEIVED
FEB 10 2004
FDR/CDER

February 6, 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

2/17/04
[Handwritten signature]

NEW CORRESP
N 2004-C

RECEIVED
FEB 10 2004
FDR/CDER

NDA 21-629: APIDRA™
HMR 1964 – Insulin glulisine (rDNA human insulin analog)
Treatment assignment errors in studies 3001 and 3004

Dear Dr. Orloff:

Reference is made to the above-mentioned New Drug Application (NDA) for APIDRA™ (HMR 1964 – insulin glulisine), which was submitted to the Agency on June 18, 2003.

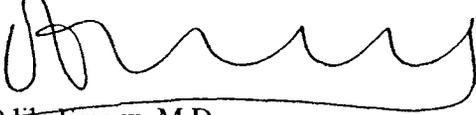
The purpose of this February 6, 2004 correspondence is to inform the Agency of treatment assignment errors identified in study 3001 and study 3004. During a review of the process for recording treatment assignment in open label studies, Aventis discovered two errors in the subjects' treatment assignments used for analysis of the data of study 3004. Because of these errors, the analyses were based on the wrong treatment group for these two patients. Two additional errors in the text of the report for study 3001 were also discovered, however, these errors do not affect the analyses of the study. No additional errors were identified in this review for any of the submitted HMR1964 studies.

For your review, this correspondence includes an Attachment that explicitly describes the nature of the errors and their effects on the reported results. Given the minimal impact of these errors on the conclusions from these studies, the study databases have not been reopened to correct these errors, and the study reports have not been amended. It is the opinion of the Sponsor that these minor errors do not affect the safety or efficacy conclusions of the studies.

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 60204d, February 4, 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,

A handwritten signature in black ink, appearing to be 'Odile Ernoux', written over a horizontal line.

Odile Ernoux, M.D.

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

Attachment: 1

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

Form Approved: OMB No. 0910-0338
Expiration Date: August 31, 2005
See OMB Statement on page 2.

**APPLICATION TO MARKET A NEW DRUG, BIOLOGIC,
OR AN ANTIBIOTIC DRUG FOR HUMAN USE**
(Title 21, Code of Federal Regulations, Parts 314 & 601)

FOR FDA USE ONLY

APPLICATION NUMBER

APPLICANT INFORMATION

NAME OF APPLICANT Aventis Pharmaceuticals, Inc.	DATE OF SUBMISSION 2/6/04
TELEPHONE NO. (Include Area Code) (908) 231-3536	FACSIMILE (FAX) Number (Include Area Code) (908) 304-6318
APPLICANT ADDRESS (Number, Street, City, State, Country, ZIP Code or Mail Code, and U.S. License number if previously issued): 200 Crossing Boulevard PO Box 6890 Bridgewater, NJ 08807-0890	AUTHORIZED U.S. AGENT NAME & ADDRESS (Number, Street, City, State, ZIP Code, telephone & FAX number) IF APPLICABLE

PRODUCT DESCRIPTION

NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER, OR BIOLOGICS LICENSE APPLICATION NUMBER (If previously issued) NDA 21-629		
ESTABLISHED NAME (e.g., Proper name, USP/USAN name) Insulin glulisine	PROPRIETARY NAME (trade name) IF ANY APIDRA™	
CHEMICAL/BIOCHEMICAL/BLOOD PRODUCT NAME (If any) 3B Lys-29B-Glu-human insulin	CODE NAME (If any) HMR 1964	
DOSAGE FORM: Injection	STRENGTHS: 100 IU/mL	ROUTE OF ADMINISTRATION: Subcutaneous

RECEIVED

(PROPOSED) INDICATION(S) FOR USE:

For treatment of adult patients with diabetes mellitus for the control of hyperglycemia

FEB 09 2004

PRODUCT DESCRIPTION

APPLICATION TYPE

(check one) NEW DRUG APPLICATION (21 CFR 314.50) ABBREVIATED NEW DRUG APPLICATION (ANDA, 21 CFR 314.94)
 BIOLOGICS LICENSE APPLICATION (21 CFR Part 601)

CDR/CDER

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

IF AN ANDA, OR 505(b)(2), 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 PENDING APPLICATION RESUBMISSION
 PRESUBMISSION ANNUAL REPORT ESTABLISHMENT DESCRIPTION SUPPLEMENT EFFICACY SUPPLEMENT
 LABELING SUPPLEMENT CHEMISTRY MANUFACTURING AND CONTROLS SUPPLEMENT OTHER

IF A SUBMISSION OF PARTIAL APPLICATION, PROVIDE LETTER DATE OF AGREEMENT TO PARTIAL SUBMISSION: _____

IF A SUPPLEMENT, IDENTIFY THE APPROPRIATE CATEGORY CBE CBE-30 Prior Approval (PA)

REASON FOR SUBMISSION

Treatment assignment errors in study 3001 and study 3004

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

NUMBER OF VOLUMES SUBMITTED NA THIS APPLICATION IS PAPER PAPER AND ELECTRONIC ELECTRONIC

ESTABLISHMENT INFORMATION (Full establishment information should be provided in the body of the Application.)

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.

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

This application contains the following items: (Check all that apply)

- 1. Index
- 2. Labeling (check one) Draft Labeling Final Printed Labeling
- 3. Summary (21 CFR 314.50 (c))
- 4. Chemistry section
 - A. Chemistry, manufacturing, and controls information (e.g., 21 CFR 314.50(d)(1); 21 CFR 601.2)
 - B. Samples (21 CFR 314.50 (e)(1); 21 CFR 601.2 (a)) (Submit only upon FDA's request)
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- 7. Clinical Microbiology (e.g., 21 CFR 314.50(d)(4))
- 8. Clinical data section (e.g., 21 CFR 314.50(d)(5); 21 CFR 601.2)
- 9. Safety update report (e.g., 21 CFR 314.50(d)(5)(vi)(b); 21 CFR 601.2)
- 10. Statistical section (e.g., 21 CFR 314.50(d)(6); 21 CFR 601.2)
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- 18. User Fee Cover Sheet (Form FDA 3397)
- 19. Financial Information (21 CFR Part 54)
- 20. OTHER (Specify) Treatment assignment errors in study 3001 and study 3004

CERTIFICATION

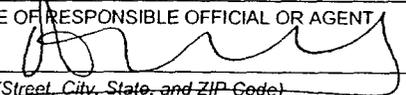
I agree to update this application with new safety information about the product that may reasonably affect the statement of contraindications, warnings, precautions, or adverse reactions in the draft labeling. I agree to submit safety update reports as provided for by regulation or as requested by FDA. If this application is approved, I agree to comply with all applicable laws and regulations that apply to approved applications, including, but not limited to the following:

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5. Regulations on making changes in application in FD&C Act Section 506A, 21 CFR 314.71, 314.72, 314.97, 314.99, and 601.12.
6. Regulations on Reports in 21 CFR 314.80, 314.81, 600.80, and 600.81.
7. Local, state and Federal environmental impact laws

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The data and information in this submission have been reviewed and, to the best of my knowledge are certified to be true and accurate.

Warning: A willfully false statement is a criminal offense, U.S. Code, title 18, section 1001.

SIGNATURE OF RESPONSIBLE OFFICIAL OR AGENT 	TYPED NAME AND TITLE Odile Ernoux, M.D., U.S. Regulatory Liaison	DATE: Feb 6, 2004
ADDRESS (Street, City, State, and ZIP Code) Aventis Pharmaceuticals, Inc.; 200 Crossing Boulevard, PO Box 6890; Bridgewater, NJ 08807-0890		Telephone Number (908) 231-3536

Public reporting burden for this collection of information is estimated to average 24 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:

Department of Health and Human Services Food and Drug Administration R, HFD-99 1401 Rockville Pike Rockville, MD 20852-1448	Food and Drug Administration CBER, HFM-94 12420 Parklawn Dr., Room 3046 Rockville, MD 20852	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.
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ATTACHMENT

Study 3001:

The following footnote a) to the flow chart in Section 6 of the Clinical Study Report states that 3 subjects were treated differently than randomized:

“3 subjects were treated differently than randomized: subjects 0807/14 and 0911/23 were randomized to glulisine but treated with lispro, and subject 0807/21 was randomized to lispro but treated with glulisine. Subjects were counted and analyzed as treated and not as randomized.”

This footnote is in error for subjects 0911/23 and 0807/21. Actually, these subjects were treated as randomized and analyzed as randomized and treated. The only error is the above-mentioned footnote. No other data or results are affected by this error.

The cause of the error was found to be as follows: On the randomization CRF, it was required to record both the randomization number provided by the IVRS system and the corresponding treatment group assignment. On a separate CRF, the investigator had to enter the treatment that was actually given to the subject, and on another drug dispensing CRF the lot numbers of the actual insulin cartridges dispensed to the patient were recorded. In the 2 cases above, the investigators had made an error in transcribing the randomization number from the IVRS fax sheet into the CRF, while the treatment assignments had been entered correctly and matched the treatments actually dispensed to the 2 patients. Thus, according to the IVRS randomization schedule, these two subjects received treatment that was consistent with the treatment assignment.

During the preparation of the study report, the treatment assignment “as randomized” was determined from the randomization numbers entered into the CRF. The two wrongly transcribed randomization numbers indicated that the two subjects had been randomized to the treatment *opposite* that which they had actually received, resulting in the respective statements in the above-mentioned footnote. Since all other analyses are based on information derived from the CRF recording the treatment received, no other data listings, tables, results, or conclusions other than the above-mentioned footnote are affected by this error.

**APPEARS THIS WAY
ON ORIGINAL**

Study 3004:

In study 3004, two subjects were erroneously analyzed and reported with a treatment assignment different from what they had been randomized to and had received. Subject # 4154/05 is reported as randomized to and being treated with regular insulin (RHI), whereas the subject was actually randomized to and treated with pre-meal glulisine. Subject # 4210/12 is reported as randomized to and being treated with pre-meal glulisine, whereas the subject was actually randomized to and treated with RHI.

In these two cases, the investigators had entered the correct random number into the randomization CRF and had dispensed the medication correctly as randomized to the patients. However, they had erroneously marked an incorrect treatment assignment on the randomization CRF. The reporting error resulted from using the treatment assignment as marked on the randomization CRF as the subjects' treatment assignment for data analysis and reporting.

Unfortunately, this error was only detected after submission of the NDA and the 120-day safety update.

Impact analyses with the correct treatment assignments for these two subjects were performed. It is the conclusion of the Sponsor that these errors do not alter the safety or efficacy conclusions of the 3004 study. However, due to the nature of this error, all efficacy and safety tables are affected to a minor degree by these errors.

A summary of the impact of these errors on the safety and primary efficacy analysis is provided below.

Safety Analysis:

No serious adverse event or severe/serious hypoglycemic episodes had been observed in either subject. Each subject had 1 non-serious, non-associated adverse event, which has consequently been counted under the wrong treatment:

- 4210/12 (analyzed as treated with glulisine, actually treated with RHI) – reported an adverse event in the Infections and infestations system organ class (**Influenza**)
- 4154/05 (analyzed as treated with RHI, actually treated with glulisine) – reported an adverse event in the Musculoskeletal and connective tissue disorders system organ class (**Ligament disorder NOS**)

Aventis does not consider these changes to affect the safety profile of glulisine.

Efficacy Analysis:

A summary of the minor changes to the key efficacy analyses are listed in the following tables. Impacts are both shaded and underlined in the original tables.

Table 1 – GHb (%): change from baseline at endpoint, ITT population (N=801)

Timepoint	Premeal Glulisine (N=268)	Postmeal Glulisine (N=276)	Regular insulin (N=257)	Difference		
				Adjusted mean	98.33% CI	p-value ^a
Mean baseline	7.73	7.70	7.64			
Mean endpoint	7.46	7.58	7.52			
Mean change from baseline at endpoint	-0.27	-0.12	-0.12			
Postmeal glulisine vs. Regular						
Adjusted mean change from baseline at endpoint ^b		-0.11	-0.13	0.02	(-0.11; 0.16)	0.6698
Premeal glulisine vs. Regular						
Adjusted mean change from baseline at endpoint ^b	-0.26		-0.13	-0.13	(-0.26; 0.01)	0.0234
Postmeal vs. Premeal glulisine						
Adjusted mean change from baseline at endpoint ^b	-0.26	-0.11		0.15	(0.02; 0.29)	0.0062

^a Statistical significance is shown if p<0.0167.

^b p-values and adjusted means from ANCOVA model (ANOVA for baseline).

Table 1 Revised – GHb (%): change from baseline at endpoint, ITT population (N=801)

Timepoint	Premeal Glulisine (N=268)	Postmeal Glulisine (N=276)	Regular insulin (N=257)	Difference		
				Adjusted mean	98.33% CI	p-value ^a
Mean baseline	7.72	7.70	7.65			
Mean endpoint	7.45	7.58	7.53			
Mean change from baseline at endpoint	-0.27	-0.12	-0.12			
Postmeal glulisine vs. Regular						
Adjusted mean change from baseline at endpoint ^b		-0.11	-0.13	0.02	(-0.11; 0.16)	0.6694
Premeal glulisine vs. Regular						
Adjusted mean change from baseline at endpoint ^b	-0.26		-0.13	-0.13	(-0.26; 0.01)	0.0234
Postmeal vs. Premeal glulisine						
Adjusted mean change from baseline at endpoint ^b	-0.26	-0.11		0.15	(0.02; 0.29)	0.0062

^a Statistical significance is shown if p<0.0167.

^b p-values and adjusted means from ANCOVA model (ANOVA for baseline).

Table 2 – GHb (%): change from baseline at endpoint, PP population (N=741)

Treatment	Premeal Glulisine (N=249)	Postmeal Glulisine (N=260)	Regular insulin (N=232)	Difference		
				Adjusted mean	98.33% CI	p-value ^a
Baseline	7.74	7.70	7.63			
Mean endpoint	7.45	7.59	7.52			
Mean change from baseline at endpoint	-0.29	-0.11	-0.11			
Postmeal glulisine vs. Regular						
Adjusted mean change from baseline at endpoint ^b		-0.11	-0.12	0.01	(-0.13; 0.16)	0.8585
Premeal glulisine vs. Regular						
Adjusted mean change from baseline at endpoint ^b	-0.27		-0.12	-0.15	(-0.30; -0.01)	0.0115
Postmeal vs. Premeal glulisine						
Adjusted mean change from baseline at endpoint ^b	-0.27	-0.11		0.17	(0.02; 0.31)	0.0058

^a Statistical significance is shown if p<0.0167.

^b p-values and adjusted means from ANCOVA model (ANOVA for baseline).

Table 2 Revised – GHb (%): change from baseline at endpoint, PP population (N=741)

Treatment	Premeal Glulisine (N=248)	Postmeal Glulisine (N=260)	Regular insulin (N=233)	Difference		
				Adjusted mean	98.33% CI	p-value ^a
Baseline	7.74	7.70	7.64			
Mean endpoint	7.45	7.59	7.52			
Mean change from baseline at endpoint	-0.29	-0.11	-0.12			
Postmeal glulisine vs. Regular						
Adjusted mean change from baseline at endpoint ^b		-0.11	-0.12	0.01	(-0.13; 0.16)	0.8550
Premeal glulisine vs. Regular						
Adjusted mean change from baseline at endpoint ^b	-0.27		-0.12	-0.15	(-0.30; -0.01)	0.0118
Postmeal vs. Premeal glulisine						
Adjusted mean change from baseline at endpoint ^b	-0.27	-0.11		0.17	(0.02; 0.31)	0.0059

^a Statistical significance is shown if p<0.0167.

^b p-values and adjusted means from ANCOVA model (ANOVA for baseline).

In the entire 3004 clinical study report, there were two instances in which p-values switched from non-significant to significant (e.g. >0.0167 to <0.0167). These instances occurred in secondary efficacy variables and only one of them occurred post randomization.

- Blood glucose excursion at breakfast at week 12 (PP population), comparison between premeal and postmeal glulisine: $p=0.0191$ in CSR (adjusted means: premeal glulisine: 0.17 mmol/L, postmeal glulisine: 0.87 mmol/L) vs. $p=0.0164$ in revised table (adjusted means: premeal glulisine 0.16 mmol/L, postmeal glulisine: 0.87 mmol/L). These data are found in Table 11-67 in the CSR.
- Subjects with at least 1 symptomatic hypoglycemic episode and a corresponding blood glucose value <2.0 mmol/L during the screening/run-in phase (PP population), comparison between premeal and postmeal glulisine: $p=0.0165$ in CSR (percentage of subjects: premeal glulisine: 30.1%, postmeal glulisine: 39.6%) vs. $p=0.0172$ in revised table (percentage of subjects: premeal glulisine: 30.2%, postmeal glulisine: 39.6%). These data are found in Table 11-83 in the CSR.

The reduction of 0.01 mmol/L in the premeal glulisine group, which contributes to the altered p-value, is minimal and not deemed to be of clinical relevance. In addition, it is noted in the CSR that premeal glulisine provides statistically superior post-breakfast glycemic control relative to postmeal glulisine administration. Thus, this shift in p-value does not alter or contradict the existing CSR.

In the screening/run-in period, all subjects were treated with regular human insulin as the mealtime insulin. Thus, the switch from non-significant to significant difference in the incidence of symptomatic hypoglycemic episodes between subjects ultimately randomized to receive premeal glulisine or postmeal glulisine occurred while all subjects were receiving regular human insulin. In addition, the magnitude of the change in the difference in the incidences is minimal.

**APPEARS THIS WAY
ON ORIGINAL**

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FEB 06 2004

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ORIGINAL



February 5, 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

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FEB 09 2004

FDR/CDER N-000-000

NDA 21-629: APIDRA™
HMR 1964 – Insulin glulisine (rDNA human insulin analog)
Safety update report

2/17/04

Dear Dr. Orloff:

Reference is made to the above-mentioned New Drug Application (NDA) for APIDRA™ (HMR 1964 – insulin glulisine), which was submitted to the Agency on June 18, 2003.

The purpose of this February 5, 2004 correspondence is to submit a safety update report for the APIDRA™ NDA. In conformance with 21 CFR 314.50(d)(5)(vi)(b), Aventis Pharmaceuticals Inc. submitted the 120-day safety update for the APIDRA™ NDA on November 4, 2003. Included in this safety update were the following final data not previously reported in the original NDA: final clinical study reports for Phase III studies 3011 and 3012, and final data for Phase III study 3005. Also included in the 120-day safety update were pooled analyses that updated the Summary of Clinical Safety to incorporate data from studies 3011, 3012, and 3005. Between the time of the 120-day safety update submission and January 15, 2004, there have been no serious adverse events reported in the pharmacovigilance database, and no subjects have received APIDRA™ treatment. Also, there is no updated information regarding preclinical studies. For the above-mentioned reporting period, therefore, there is no new safety information to report for APIDRA™.

This submission is fully electronic. 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 60129d, January 29, 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

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

Form Approved: OMB No. 0910-0338
Expiration Date: August 31, 2005
See OMB Statement on page 2.

**APPLICATION TO MARKET A NEW DRUG, BIOLOGIC,
OR AN ANTIBIOTIC DRUG FOR HUMAN USE**
(Title 21, Code of Federal Regulations, Parts 314 & 601)

FOR FDA USE ONLY

APPLICATION NUMBER

APPLICANT INFORMATION

NAME OF APPLICANT Aventis Pharmaceuticals, Inc.	DATE OF SUBMISSION 2/5/04
TELEPHONE NO. (Include Area Code) (908) 231-3536	FACSIMILE (FAX) Number (Include Area Code) (908) 304-6318
APPLICANT ADDRESS (Number, Street, City, State, Country, ZIP Code or Mail Code, and U.S. License number if previously issued): 200 Crossing Boulevard PO Box 6890 Bridgewater, NJ 08807-0890	AUTHORIZED U.S. AGENT NAME & ADDRESS (Number, Street, City, State, ZIP Code, telephone & FAX number) IF APPLICABLE RECEIVED FEB 06 2004 CDR/CDER

PRODUCT DESCRIPTION

NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER, OR BIOLOGICS LICENSE APPLICATION NUMBER (If previously issued) NDA 21-629		
ESTABLISHED NAME (e.g., Proper name, USP/USAN name) Insulin glulisine	PROPRIETARY NAME (trade name) IF ANY APIDRA™	
CHEMICAL/BIOCHEMICAL/BLOOD PRODUCT NAME (If any) 3B Lys-29B-Glu-human insulin	CODE NAME (If any) HMR 1964	
DOSAGE FORM: Injection	STRENGTHS: 100 IU/mL	ROUTE OF ADMINISTRATION: Subcutaneous
(PROPOSED) INDICATION(S) FOR USE: For treatment of adult patients with diabetes mellitus for the control of hyperglycemia		

APPLICATION TYPE

(check one) <input checked="" type="checkbox"/> NEW DRUG APPLICATION (21 CFR 314.50)		<input type="checkbox"/> ABBREVIATED NEW DRUG APPLICATION (ANDA, 21 CFR 314.94)	
<input type="checkbox"/> BIOLOGICS LICENSE APPLICATION (21 CFR Part 601)			
IF AN NDA, IDENTIFY THE APPROPRIATE TYPE <input checked="" type="checkbox"/> 505 (b)(1)		<input type="checkbox"/> 505 (b)(2)	
IF AN ANDA, OR 505(b)(2), 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)			
<input type="checkbox"/> ORIGINAL APPLICATION	<input type="checkbox"/> AMENDMENT TO PENDING APPLICATION	<input type="checkbox"/> RESUBMISSION	
<input type="checkbox"/> PRESUBMISSION	<input type="checkbox"/> ANNUAL REPORT	<input type="checkbox"/> ESTABLISHMENT DESCRIPTION SUPPLEMENT	<input type="checkbox"/> EFFICACY SUPPLEMENT
<input type="checkbox"/> LABELING SUPPLEMENT	<input type="checkbox"/> CHEMISTRY MANUFACTURING AND CONTROLS SUPPLEMENT	<input checked="" type="checkbox"/> OTHER	
IF A SUBMISSION OF PARTIAL APPLICATION, PROVIDE LETTER DATE OF AGREEMENT TO PARTIAL SUBMISSION: _____			
IF A SUPPLEMENT, IDENTIFY THE APPROPRIATE CATEGORY <input type="checkbox"/> CBE <input type="checkbox"/> CBE-30 <input type="checkbox"/> Prior Approval (PA)			
REASON FOR SUBMISSION safety update correspondence for APIDRA™ NDA			
PROPOSED MARKETING STATUS (check one) <input checked="" type="checkbox"/> PRESCRIPTION PRODUCT (Rx)		<input type="checkbox"/> OVER THE COUNTER PRODUCT (OTC)	
NUMBER OF VOLUMES SUBMITTED NA	THIS APPLICATION IS <input type="checkbox"/> PAPER <input type="checkbox"/> PAPER AND ELECTRONIC <input checked="" type="checkbox"/> ELECTRONIC		
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CERTIFICATION

I agree to update this application with new safety information about the product that may reasonably affect the statement of contraindications, warnings, precautions, or adverse reactions in the draft labeling. I agree to submit safety update reports as provided for by regulation or as requested by FDA. If this application is approved, I agree to comply with all applicable laws and regulations that apply to approved applications, including, but not limited to the following:

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5. Regulations on making changes in application in FD&C Act Section 506A, 21 CFR 314.71, 314.72, 314.97, 314.99, and 601.12.
6. Regulations on Reports in 21 CFR 314.80, 314.81, 600.80, and 600.81.
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SIGNATURE OF RESPONSIBLE OFFICIAL OR AGENT 	TYPED NAME AND TITLE Odile Ernoux, M.D., U.S. Regulatory Liaison	DATE: Feb 5, 2004
ADDRESS (Street, City, State, and ZIP Code) Aventis Pharmaceuticals, Inc.; 200 Crossing Boulevard, PO Box 6890; Bridgewater, NJ 08807-0890		Telephone Number (908) 231-3536

Public reporting burden for this collection of information is estimated to average 24 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:

Department of Health and Human Services
and Drug Administration
_R, HFD-99
1401 Rockville Pike
Rockville, MD 20852-1448

Food and Drug Administration
CDER, HFM-94
12420 Parklawn Dr., Room 3046
Rockville, MD 20852

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Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation ODE II

FACSIMILE TRANSMITTAL SHEET

DATE: February 4, 2004

To: Odile Ernoux, M.D.	From: Julie Rhee
Company: Aventis Pharmaceuticals Inc.	Division of Metabolic and Endocrine Drug Products
Fax number: (908) 304-6318	Fax number: (301) 443-9282
Phone number: (908) 231-3536	Phone number: (301) 827-6424
Subject: NDA 21-629 Apidra	

Total no. of pages including cover: 2

Comments:

Additional clinical information request

Document to be mailed: YES NO

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

Date of submission: June 18, 2003

Additional Clinical Information Request

1. Please apply observational study methods to adjust for the claimed imbalance at baseline in Study 3001 and demonstrate the effect of adjustment on outcome of concern (i.e., coronary events). (This request has been previously submitted.)
2. The definition for severe hypoglycemia required the assistance of another person and (a) glucose concentration ≤ 36 mg/dl (originally ≤ 50 mg/dl) or (b) response to oral carbohydrate, glucose infusion, or glucagon administration. What number and percent of the patients randomized to the two treatment groups did not require the assistance of another person but had symptomatic hypoglycemia defined by glucose concentration ≤ 50 mg/dl or symptomatic nocturnal hypoglycemia defined by a glucose concentration ≤ 50 mg/dl?
3. For studies 3001, 3002, 3005, please provide the total number and percent of patients and events in each treatment group who presented with severe symptomatic hypoglycemia and severe nocturnal hypoglycemia in months 1 through 3, so that these data can be compared to the 3-month trials.
4. For patients with severe symptomatic hypoglycemia, please provide a table indicating number of patients with 1, 2, 3, 4 or more episodes of hypoglycemia in the glulisine-treated group and the comparator group, for studies 3001, 3011, 3002, 3012, 3004, 3005, 3006
5. Please provide a similar table for patients with severe nocturnal symptomatic hypoglycemia, indicating the number of patients with 1, 2, 3, 4 or more episodes of hypoglycemia in the glulisine-treated group and the comparator group, for studies 3001, 3011, 3002, 3012, 3004, 3005, 3006
6. The protocols state that the investigators and patients were blinded to the GHb results during the studies. Were additional HbA1c measurements obtained at the study sites that were available to investigators and patients? If so, were these measurements equally distributed between the treatment groups?
7. What is the timing between the last daily injection of rapid acting insulin and any nocturnal glucose concentration ≤ 70 mg/dl for the two treatment groups in Study 3001? How many patients in each treatment group had at least one nocturnal glucose concentration ≤ 70 mg/dl?

8a. For patients identified with severe nocturnal hypoglycemia in Study 3001 (Type 1 diabetes mellitus – comparison of glulisine and lispro), please provide the following information for each individual patient and also as the mean value per treatment group:

- Timing and dose of last rapid acting insulin injection and episode of severe nocturnal hypoglycemia
- Total daily rapid acting insulin dose
- Number of rapid acting insulin injections per day
- Timing and dose of glargine insulin injection and episode of severe nocturnal hypoglycemia
- Total daily glargine insulin dose
- Total insulin dose at baseline and endpoint
- Creatinine concentration
- GHb at baseline and endpoint
- Patient ID, age, sex, duration of DM
- Total number of symptomatic and severe symptomatic hypoglycemia episodes during the study
- Study day of severe nocturnal hypoglycemia and number of symptomatic and severe symptomatic hypoglycemia episodes that preceded it during the study

8b. What is the sponsor's explanation for the imbalance of severe nocturnal hypoglycemia between the two treatment groups in Study 3001?

9. For the treatment emergent adverse event "retinal disorder," provide table listing the following data:

- Patient ID/Study
- Age
- Sex
- Duration of Diabetes Mellitus
- GHb at baseline and endpoint
- Additional specific information regarding the retinal AE

10. Has this NDA been submitted to any other regulatory board? If so, when and what has been the action taken?

**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

2/4/04 10:20:18 AM



Food and Drug Administration
Rockville MD 20857

FEB 2 2004

Mark A. Quigley, R.Ph., Ph.D.
Vice President, Global Quality Assurance, Compliance & Regulatory CMC
Aventis Pharmaceuticals
Mail Code: BX4-309C
200 Crossing Boulevard
P.O. Box 6890
Bridgewater, New Jersey 08807-0890

Dear Dr. Quigley:

Between November 18 and December 8, 2003, Ms. Jean M. Kelahan and Mr. Marcelo O. Mangalindan, Jr., representing the Food and Drug Administration (FDA), conducted an inspection of Aventis Pharmaceuticals' management procedures of the following clinical studies of the investigational drug Apidra™ (insulin glulisine [rDNA origin]).

HMR1964A/3002, "26-Week, Multinational, Multicenter, Controlled, Open, 1:1 Randomized, Parallel Clinical Trial Comparing HMR1964 with Regular Human Insulin Injected Subcutaneously in Subjects with Type 2 Diabetes Mellitus Also Using NPH Insulin Which Will Lead into a Comparative 26-Week Safety Extension Study (HMR1964A/3012)"

HMR1964A/3004, "12-Week, Multinational, Multicenter, Controlled, Open, 1:1:1 Randomized, Parallel Clinical Trial to Assess Noninferiority Between Pre-and Post-Meal Administration of HMR1964 and Pre-Meal Regular Human Insulin in Subjects with Type 1 Diabetes Mellitus Receiving Insulin Glargine as the Basal Insulin Therapy"

This inspection is a part of FDA's Bioresearch Monitoring Program, which includes inspections designed to evaluate the conduct of research and to ensure that the rights, safety, and welfare of the human subjects of those studies have been protected.

From our evaluation of the establishment inspection report and the documents submitted with that report, we conclude that you adhered to the applicable statutory requirements and FDA regulations governing the conduct of clinical investigations and the protection of human subjects.

Page 2 – Mark A. Quigley, R.Ph., Ph.D. – Aventis Pharmaceuticals

We appreciate the cooperation shown Investigators Kelahan and Mangalindan 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/

Khin Maung U, M.D.
Branch Chief
Good Clinical Practice Branch I, HFD-46
Division of Scientific Investigations
Office of Medical Policy
Center for Drug Evaluation and Research
7520 Standish Place, Room 125
Rockville, MD 20855

cc:

HFA-224

HFD-510 / Document Room: NDA 21-629 Apidra™ (insulin glulisine)

HFD-510 / Review Division Director: David Orloff, M.D.

HFD-510 / Review Division Medical Officer: Joanna Zawadzki, M.D.

HFD-510 / PM: Julie Rhee

HFD-45 / Division File/ Reading File

HFD-47 / Chron File

HFD-46 / U / Slavin

HFD-47 / GCPB I File #10876

HFR-CE350 DIB (Amador)

HFR-CE3565 BIMO MONITOR (Isbill)

HFR-CE3565 FIELD INVESTIGATORS (Kelahan/Mangalindan)

GCF-1 Seth Ray

FEI#: 2222017

CIB (GCP I): 10876

FACTS#: 470432

Field Classification: VAI

Headquarters Classification:

<input checked="" type="checkbox"/>	1)	NAI	
<input type="checkbox"/>	2)	VAI	no response required
<input type="checkbox"/>	3)	VAI-R	response requested
<input type="checkbox"/>	4)	VAI-RR	adequate response received prior to issuance of VAI-R letter
<input type="checkbox"/>	5)	OAI-WL	warning letter

O: \\(slavin\Aventis letter)

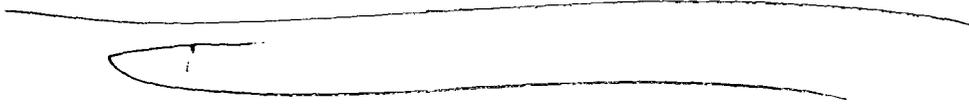
drafted : AS (1/23/04)

reviewed: KMU (1/29/04)

finald: SG: (1/29/04)

Reviewer's Note to file #10876: Inspection of Aventis Pharmaceuticals (Ref: NDA 21-629).

This was a routine pre-approval sponsor inspection. The inspection focused on the sponsor's management of clinical trials 3002 and 3004. FDA investigators reviewed qualifications of clinical investigators/monitors for 10 sites for each protocol. Four of 10 sites audited for protocol 3004, were deficient for not having clinical investigator financial disclosure information. One hundred and twenty CRFs for protocol 3002 and 50 CRFs for protocol 3004 were audited. The number of subjects reported as randomized and treated, matched the numbers in the tables of the final study reports. The primary issue noted during the inspection pertained to



ASCI file reports were the same GHb results reported in the 3002 and 3004 final reports. A Form FDA-483 was not issued. Inspection of the sponsor is classified NAI.

**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/

Khin U
2/5/04 10:17:41 AM



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

FEB 2 2004

Dear Dr. _____

On November 18, 2003, Mr. Carl J. Montgomery, representing the Food and Drug Administration (FDA), conducted an investigation of your monitoring procedures for the following clinical investigation (protocol #HMR1964A/3002 entitled: "26-Week, Multinational, Multicenter, Controlled, Open, 1:1 Randomized, Parallel Clinical Trial Comparing HMR1964 with Regular Human Insulin Injected Subcutaneously in Subjects with Type 2 Diabetes Mellitus Also Using NPH Insulin and Which Will Lead into a Comparative 26-Week Safety Extension Study (HMR1964A/3012)" of the investigational drug Apidra™ (insulin glulisine [rDNA origin]), performed for Aventis Pharmaceuticals.

This inspection is a part of FDA's Bioresearch Monitoring Program, which includes inspections designed to evaluate the conduct of research and to ensure that the rights, safety, and welfare of the human subjects of those studies have been protected.

From our evaluation of the establishment inspection report and the documents submitted with that report, we conclude that you adhered to the applicable statutory requirements and FDA regulations governing the conduct of clinical investigations and the protection of human subjects.

We appreciate the cooperation shown Investigator Montgomery 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/

Khin Maung U, M.D.
Branch Chief
Good Clinical Practice Branch I, HFD-46
Division of Scientific Investigations
Office of Medical Policy
Center for Drug Evaluation and Research
7520 Standish Place, Room 125
Rockville, MD 20855

cc:

HFA-224

HFD-510 / Document Room: NDA 21-629 Apidra™ (insulin glulisine)

HFD-510 / Review Division Director: David Orloff, M.D.

HFD-510 / Review Division Medical Officer: Joanna Zawadzki, M.D.

HFD-510 / PM: Julie Rhee

HFD-45 / Division File/ Reading File

HFD-47 / Chron File

HFD-46 / U / Slavin

HFD-47 / GCPB I File #10209

HFR-SW350 DIB (Thorsky)

HFR-SW350 BIMO MONITOR (Montgomery)

HFR-SW350 FIELD INVESTIGATOR (same as BIMO Monitor)

GCF-1 Seth Ray

FEI#: 3002929455

CIB (GCP I): 10209

FACTS#: 470432

Field Classification: NAI

Headquarters Classification:

- | | | | |
|----------|----|--------|--|
| <u>X</u> | 1) | NAI | |
| _____ | 2) | VAI | no response required |
| _____ | 3) | VAI-R | response requested |
| _____ | 4) | VAI-RR | adequate response received prior to issuance of VAI-R letter |
| _____ | 5) | OAI-WL | warning letter |

drafted: AS (1/30/04)

reviewed: KMU (1/30/04)

finalized: SG: (1/30/04)

Reviewer's Note to file #10209: Inspection of _____ (Ref: NDA 21-629).

This was a routine pre-approval CRO inspection conducted in support of NDA 21-629. The sponsor, Aventis, transferred monitoring responsibilities to _____ Studies 3002 and 3004 were audited in support of this NDA. Dr. _____ site (40 subjects) was audited for study 3002 and Dr. _____ site (39 subjects) was audited for study 3004.

It was noted during the inspection at _____ office monitored study 3004; therefore, the inspection focused on study 3002 which was monitored by the _____ office. The FDA investigator reviewed the Trial Master File for Dr. _____ site. No deviations from FDA regulations were noted.

A Form FDA-483 was not issued. Inspection of the CRO is classified as NAI.

Note: the inspection of Aventis Pharmaceuticals was also classified as NAI.

MEMORANDUM

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

DATE: January 15, 200~~3~~⁴

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 of the Patient Labeling for Apidra (insulin glulisine [recombinant DNA origin], NDA 21-629)

The attached patient labeling (clean copies) represent the revised risk communication materials for Apidra (insulin glulisine [recombinant DNA origin], NDA 21-629). It has been reviewed by our office (DSRCS and DMETS) and by DDMAC. We have simplified the wording, made it consistent with the PI, removed promotional language and other unnecessary information (the purpose of patient information leaflets is to enhance appropriate use and provide important risk information about medications), and put it in the format that we are recommending for all patient information. Our proposed changes are known through research and experience to improve risk communication to a broad audience of varying educational backgrounds. These revisions are based on draft labeling submitted by the sponsor on June 18, 2003. Patient information should always be consistent with the prescribing information. All future changes to the PI should also be reflected in the PPI.

Comments to the review division are bolded, underlined and italicized. We can provide marked-up and clean copies of the revised documents in Word if requested by the review division.

We also have the following comment:

ODS/DSRCS has noted 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 low literacy readers. The review division may want to consider initiating class PPI labeling in the future for diabetic products utilizing the following suggestions:

1. 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.
2. Simplify the vocabulary and sentence structure for low literacy readers. A 6th to 8th grade reading comprehension level is optimal for all patient materials.
3. 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.
4. Remove any promotional language per DDMAC guidelines.

Please let us know if you have any questions.

**APPEARS THIS WAY
ON ORIGINAL**

Patient Information
APIDRA™ (uh-PEE-druh) 10 mL vial (1000 units per vial) 100 units per mL (U-100)

(insulin glulisine [recombinant DNA origin] injection)

Read the Patient Information that comes with APIDRA before you start using it and each time you get a refill. There may be new information. This leaflet does not take the place of talking with your healthcare provider about your condition or treatment. If you have questions about APIDRA or about diabetes, talk with your healthcare provider.

What is the most important information I should know about APIDRA?

Do not change the insulin you are using without talking to your healthcare provider. Any change in insulin strength, manufacturer, type (regular, NPH, analog), or species (animal, human) may need a change in the dose. This dose change may be needed right away or later on during the first several weeks or months on the new insulin. Doses of oral anti-diabetic medicines may also need to change, if your insulin is changed.

You must test your blood sugar levels while using APIDRA. Your healthcare provider will tell you how often you should test your blood sugar level.

APIDRA comes as U-100 insulin. One milliliter (mL) of U-100 contains 100 units of APIDRA. (1 mL = 1 cc).

What is APIDRA?

APIDRA is a fast-acting man-made insulin that is like insulin made by your body. APIDRA is used to treat adults with diabetes for the control of high blood sugar. APIDRA starts working faster than regular insulin and does not work as long. APIDRA is used with a longer-acting or by itself as insulin pump therapy to maintain proper blood sugar control.

Your body needs insulin to turn sugar (glucose) into energy. If your body does not make enough insulin, you need to take insulin so you will not have too much sugar in your blood.

Insulin injections are important in keeping your diabetes under control. But the way you live, your diet, careful checking of your blood sugar levels, exercise, and planned physical activity, all work with your insulin to help you control your diabetes.

You need a prescription to get APIDRA. Always be sure you receive the right insulin from the pharmacy.

Who should not take APIDRA?

Do not take APIDRA if you are allergic to insulin glulisine or any of the inactive ingredients in APIDR. See the end of this leaflet for a list of the inactive ingredients.

Before starting APIDRA, tell your healthcare provider

- **about all you medical problems including if you:**
 - **have liver or kidney problems.** Your dose may need to be adjusted.
 - **are pregnant or plan to become pregnant.** It is not known if APIDRA may harm your unborn baby. It is very important to maintain control of your blood sugar levels during pregnancy. Your healthcare provider will decide which insulin is best for during your pregnancy.
 - **are breastfeeding or plan to breastfeed.** It is not known whether APIDRA passes into your milk. Many medicines, including insulin, pass into human milk, and could affect your baby. Talk to your healthcare provider about the best way to feed your baby.
- **about all the medicines you take including** prescription and non-prescription medicines, vitamins and herbal supplements. ✓ _____

How should I use APIDRA?

See the end of this leaflet for the "Instructions for Use" including the sections "How do I draw the insulin into the syringe?" and "How do I use APIDRA with an external subcutaneous insulin infusion pump?"

- Follow the instructions given by your healthcare provider about the type or types of insulin you are using. Do not make any changes with your insulin unless you have talked to your healthcare provider. Your insulin needs may change because of illness, stress, other medicines, or changes in diet or activity level. Talk to your healthcare provider about how to adjust your insulin dose.
- You should take APIDRA within 15 minutes before a meal or ✓ _____
_____) Only use APIDRA that is clear and colorless. If your APIDRA is cloudy or colored, return it to your pharmacy for a replacement.
- Follow your healthcare provider's instructions for testing your blood sugar.
- Inject APIDRA under your skin (subcutaneously) in your upper arm, abdomen (stomach area), or thigh (upper leg). Never inject it into a vein or muscle. If you use a pump, infuse APIDRA through the skin of your abdomen.
- Change (rotate) injection sites within the same body area.

What kind of syringe should I use?

- Always use a syringe that is marked for U-100 insulins. If you use the wrong syringe, you may get the wrong dose. You could get a blood sugar level that is too low or too high.
- If you are mixing APIDRA with NPH human insulin, draw APIDRA into the syringe first. Inject the mixture right away. **Do not mix APIDRA with any other type of insulin than NPH.**
- **Do not mix APIDRA with any other insulin when used in a pump.**

What can affect how much insulin I need?

Illness. Illness may change how much insulin you need. It is a good idea to think ahead and make a "sick day" plan with your healthcare provider in advance so you will be ready when this happens. Be sure to test your blood sugar more often and call your healthcare provider if you are sick.

Medicines. Many medicines can affect your insulin needs. Other medicines, include prescription and non-prescription medicines, vitamins and herbal supplements. You may need a different dose of insulin when you are taking certain other medicines. **Know all the medicines you take**, including prescription and non-prescription medicines, vitamins and herbal supplements. Keep a list of the medicines you take. Show this list to all your healthcare providers and pharmacists anytime you get a new medicine or refill. They will tell you if your insulin dose needs to be changed.

Meals. The amount of food you eat can affect your insulin needs. If you eat less food, skip meals, or eat more food than usual, you may need a different dose of insulin. Talk to your healthcare provider if you change your diet so that you know how to adjust your APIDRA and other insulin doses.

Exercise or Activity level. Exercise or activity level may change the way your body uses insulin. Check with your healthcare provider before you start an exercise program because your dose may need to be changed.

Travel. If you travel across time zones, talk with your healthcare provider about how to time your injections. When you travel, wear your medical alert identification. Take extra insulin and supplies with you.

┌ _____

_____ └

What are the possible side effects of APIDRA and other insulins?