

**CENTER FOR DRUG EVALUATION AND RESEARCH**

**Approval Package for:**

***APPLICATION NUMBER:***

**NDA 021629/S-008**

***Trade Name:*** Apidra SoloStar

***Generic Name:*** Insulin Glulisine [Rdna Origin] Injection

***Sponsor:*** Sanofi Aventis U.S., Inc.

***Approval Date:*** 02/24/2009

***Indications:*** APIDRA is a rapid acting human insulin analog indicated to improve glycemic control in adults and children with diabetes mellitus.

# CENTER FOR DRUG EVALUATION AND RESEARCH

*APPLICATION NUMBER:*  
**NDA 021629/S-008**

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**CENTER FOR DRUG EVALUATION AND  
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*APPLICATION NUMBER:*  
**NDA 021629/S-008**

**APPROVAL LETTER**



NDA 21-629/S-008

**SUPPLEMENT APPROVAL**

sanofi aventis U.S., Inc.  
Attention: Rima Nassar, Ph.D.  
Regulatory Development  
200 Crossing Boulevard, Mailstop: BX4-206A  
Bridgewater, NJ 08807

Dear Dr. Nassar:

Please refer to your supplemental new drug application dated April 21, 2006, received April 24, 2006, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Apidra (insulin glulisine [rDNA origin] injection), which provided for the addition of the Apidra SoloStar disposable injector pen.

We acknowledge receipt of your submission dated September 15, 2008, which constituted a complete response to our July 3, 2008, action letter.

We also acknowledge receipt of your submissions dated August 19, September 15, and November 10, 2008, and January 30, 2009.

During review of Supplement 015 (approved October 24, 2008) we requested via email on April 21, 2008, you to revise the multiple patient package inserts for Apidra into a single patient package insert with multiple instructions for use leaflets. Your April 24, 2008, submission requested deferring these labeling changes and combining them with Supplement 008. We approved your request, thus the vial and cartridge instruction for use leaflets are included.

We have completed our review of this application, as amended. It is approved, effective on the date of this letter, for use as recommended in the enclosed agreed-upon labeling text.

### **CONTENT OF LABELING**

As soon as possible, but no later than 14 days from the date of this letter, please submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format as described at <http://www.fda.gov/oc/datacouncil/spl.html> that is identical to the enclosed labeling text for the package insert, patient package insert, instruction for use leaflets (Apidra SoloStar Pen, Apidra Cartridge, and Apidra Vial) submitted January 30, 2009. Upon receipt, we will transmit that version to the National Library of Medicine for public dissemination. For administrative purposes, please designate this submission, "**SPL for approved NDA 21-629/S-008.**"

## **CARTON AND IMMEDIATE CONTAINER LABELS**

Submit final printed carton and container labels that are identical to the enclosed carton and immediate container labels submitted on September 15, 2008, as soon as they are available, but no more than 30 days after they are printed. Please submit these labels electronically according to the guidance for industry titled *Providing Regulatory Submissions in Electronic Format – Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications (October 2005)*. Alternatively, you may submit 12 paper copies, with 6 of the copies individually mounted on heavy-weight paper or similar material. For administrative purposes, designate this submission “**Final Printed Carton and Container Labels for approved NDA 21-629/S-008.**” Approval of this submission by FDA is not required before the labeling is used.

Marketing the product(s) with FPL that is not identical to the approved labeling text may render the product misbranded and an unapproved new drug.

## **PROMOTIONAL MATERIALS**

You may request advisory comments on proposed introductory advertising and promotional labeling. To do so, submit, in triplicate, a cover letter requesting advisory comments, the proposed materials in draft or mock-up form with annotated references, and the package insert(s) to:

Food and Drug Administration  
Center for Drug Evaluation and Research  
Division of Drug Marketing, Advertising, and Communications  
5901-B Ammendale Road  
Beltsville, MD 20705-1266

As required under 21 CFR 314.81(b)(3)(i), you must submit final promotional materials, and the package insert(s), at the time of initial dissemination or publication, accompanied by a Form FDA 2253. For instruction on completing the Form FDA 2253, see page 2 of the Form. For more information about submission of promotional materials to the Division of Drug Marketing, Advertising, and Communications (DDMAC), see [www.fda.gov/cder/ddmac](http://www.fda.gov/cder/ddmac).

Please submit one market package of the drug product when it is available.

## **LETTERS TO HEALTH CARE PROFESSIONALS**

If you issue a letter communicating important safety related information about this drug product (i.e., a “Dear Health Care Professional” letter), we request that you submit an electronic copy of the letter to both this NDA and to the following address:

MedWatch  
Food and Drug Administration  
Suite 12B05  
5600 Fishers Lane  
Rockville, MD 20857

If you have any questions, call Rachel Hartford, Regulatory Project Manager, at (301) 796-0331.

Sincerely,

*{See appended electronic signature page}*

Mary H. Parks, M.D.  
Director  
Division of Metabolism and Endocrinology Products  
Office of Drug Evaluation II  
Center for Drug Evaluation and Research

Enclosures:

Package Insert

Patient Package Insert

Instructions for Use Leaflet – Apidra SoloStar Pen

Instructions for Use Leaflet – Apidra Cartridge

Instructions for Use Leaflet – Apidra Vial

SoloStar Pen Carton

SoloStar Pen Container

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/s/

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Mary Parks  
2/24/2009 04:07:28 PM

**CENTER FOR DRUG EVALUATION AND  
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*APPLICATION NUMBER:*  
**NDA 021629/S-008**

**OTHER ACTION LETTER(S)**



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration  
Rockville, MD 20857

NDA 21-629/S-008

sanofi aventis U.S., Inc.  
Attention: Rima Nassar, Ph.D.  
Regulatory Development  
200 Crossing Boulevard, Mailstop: BX4-206A  
Bridgewater, NJ 08807

Dear Dr. Nassar:

Please refer to your supplemental new drug application dated April 21, 2006, received April 24, 2006, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Apidra (Insulin glulisine [rDNA origin] injection), which provided for the addition of the Apidra SoloStar disposable injector pen.

We acknowledge receipt of your submission dated March 3, 2008, which constituted a complete response to our January 18, 2008, action letter.

We also acknowledge receipt of your submissions dated January 25, February 20, May 1 and June 13, 23, and 30, 2008.

We also acknowledge the meeting between members of our Division, the Division of Medication Errors and Prevention, and sanofi-aventis on June 11, 2008, which was held after we completed our review of your application. At that meeting, FDA notified you that your complete response will not adequately address our concerns regarding confusion between the Lantus SoloStar and Apidra SoloStar pens. Specifically, we discussed limitations related to the design of your completed differentiation study. Therefore, your application is approvable. Before the application may be approved, however, you must address the following deficiency:

**Provide adequate evidence that the proposed name and color scheme for the pen, container, and carton labels for Apidra SoloStar will not exacerbate medication errors because of confusion with Lantus SoloStar.**

You have agreed to resolve this deficiency by conducting a new study to show that Apidra SoloStar and Lantus SoloStar are adequately differentiated. We strongly recommend that you obtain FDA agreement on the proposed study design prior to study initiation to ensure that results will be satisfactorily interpretable.

Further discussions regarding labeling will take place during the next review cycle.

If additional information relating to the safety or effectiveness of this drug becomes available, revision of the labeling may be required.

Within 10 days after the date of this letter, you are required to amend the application, notify us of your intent to file an amendment, or follow one of your other options under 21 CFR 314.110. If you do not follow one of these options, we will consider your lack of response a request to withdraw the application under 21 CFR 314.65. Any amendment should respond to all the deficiencies listed. We will not process a partial reply as a major amendment nor will the review clock be reactivated until all deficiencies have been addressed.

This product may be considered to be misbranded under the Federal Food, Drug, and Cosmetic Act if it is marketed with this change before approval of this supplemental application.

If you have any questions, call Rachel Hartford, Regulatory Project Manager, at (301) 796-0331.

Sincerely,

*{See appended electronic signature page}*

Mary H. Parks, M.D.

Director

Division of Metabolism and Endocrinology Products

Office of Drug Evaluation II

Center for Drug Evaluation and Research

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/s/

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Mary Parks

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NDA 21-629/S-008

sanofi-aventis U.S. LLC  
Attention: Michael Lutz, M.Sc., MBA  
US Regulatory Development  
200 Crossings Boulevard, Mailstop: BX4-209A  
Bridgewater, NJ 09907

Dear Mr. Lutz:

Please refer to your supplemental new drug application dated April 21, 2006, received April 24, 2006, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Apidra (Insulin glulisine [rDNA origin] injection), which provided for the addition of the Apidra SoloStar disposable injector pen.

We acknowledge receipt of your submission dated September 14, 2007, which constituted a complete response to our August 24, 2006, action letter.

We have completed our review of this application, and it is approvable. Before the application may be approved, however, you must address the following deficiencies:

1. [REDACTED] (b) (4)

We are concerned that the currently proposed name, pen, container and carton labels introduce vulnerability to confusion between Apidra SoloStar and Lantus SoloStar that could lead to serious medication errors, if approved. [REDACTED] (b) (4)

You state in your cover letter that "...the combination of color and design for Lantus...and Apidra...have been agreed upon previously between the Agency and sanofi-aventis. These color/design combinations were approved by the Agency for Lantus on April 20, 2000 (NDA 21-081) and for Apidra on December 20, 2005 (NDA 21-629/S-001 and NDA 21-629/S002). [REDACTED] (b) (4)

[REDACTED] However, we have received numerous postmarketing reports of confusion between Lantus and Apidra [REDACTED] (b) (4) on their labels as the SoloStar products. The root cause analysis of the medication errors has consistently indicated that the errors are the result of similar packaging and color presentation. [REDACTED] (b) (4)

(b) (4) You will need to perform studies to provide us with reasonable assurance that the approval of the revised color schemes of the Apidra pen device and label will not exacerbate medication errors.

Based on our reviews of the postmarketing data and (b) (4) we have concluded that adding "SoloStar" to Apidra increases the similarity to Lantus SoloStar and may exacerbate the existing confusion with the Apidra and Lantus products, particularly in conjunction with the physical and visual similarity of the pen products. (b) (4)

(b) (4)  
However, if you choose this latter option, you will need to perform studies to provide us with reasonable assurance that the approval of the SoloStar name will not exacerbate medication errors.

**2. Include a statement in the Instruction Leaflet that the plunger will not move down to the end of the barrel when the drug is administered.**

Revision of the Instruction Leaflet is based on a postmarketing report of a patient who injected three times (255 units) the prescribed dose resulting in admission to the emergency room. The patient expected the plunger to drop to the end of the barrel once administered as occurs with the plunger in syringes.

Please submit revised labeling.

If additional information relating to the safety or effectiveness of this drug becomes available, revision of the labeling may be required.

Within 10 days after the date of this letter, you are required to amend the application, notify us of your intent to file an amendment, or follow one of your other options under 21 CFR 314.110. If you do not follow one of these options, we will consider your lack of response a request to withdraw the application under 21 CFR 314.65. Any amendment should respond to all the deficiencies listed. We will not process a partial reply as a major amendment nor will the review clock be reactivated until all deficiencies have been addressed.

This product may be considered to be misbranded under the Federal Food, Drug, and Cosmetic Act if it is marketed with this change before approval of this supplemental application.

If you have any questions, call Rachel Hartford, Regulatory Project Manager, at (301) 796-0331.

Sincerely,

*{See appended electronic signature page}*

Mary H. Parks, M.D.

Director

Division of Metabolism and Endocrinology Products

Office of Drug Evaluation II

Center for Drug Evaluation and Research

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/s/

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Mary Parks  
1/18/2008 06:17:53 AM



NDA 21-081/S-024  
NDA 21-629/S-008

sanofi-aventis U.S. LLC  
Attention: Michael Lutz  
US Regulatory Development  
200 Crossing Boulevard, PO Box 6890  
Bridgewater, ND 08807-0890

Dear Mr. Lutz:

Please refer to your supplemental new drug applications dated April 21, 2006, received April 24, 2006, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for

NDA 21-018/S-024 Lantus (insulin glargine [rDNA origin]) Injection  
NDA 21-629/S-008 Apidra (insulin glulisine [rDNA origin]) Injection.

These supplemental new drug applications provide for the addition of disposable injector pens, Lantus SoloStar and Apidra SoloStar.

We completed our review of these applications, and they are approvable. Before the applications may be approved, however, you must address the following deficiencies:

#### **CHEMISTRY, MANUFACTURING, AND CONTROLS**

1. For each 3 mL drug product cartridge (NDA 21-018 and NDA 21-629) in the SoloStar device, submit six months of long term stability data. (b) (4)

#### **DEVICE ISSUES**

2. Please describe the method by which the SoloStar indicates that the injection has been completed.
3. You have indicated that the dialing mechanism allows dosage in 1 insulin unit increments and provides a maximum of 80 insulin units in one dosing. Describe how the design limits dosing to 80 units. Also describe the testing that has been conducted on the dose setting mechanism. Specifically, has testing been performed to assess functionality if the user rapidly turns the dial or if the user turns the dial clockwise past 80 units and then attempts to turn the dial counterclockwise?
4. Describe the method and mechanism for ensuring that the last dose delivered from the insulin cartridge satisfies requirements for dose accuracy.

5. Indicate whether the device has a safety mechanism to prevent accidental firing.
6. Identify the pen injector needles that are compatible with the SoloStar in your Instructions for Use.
7. You state that the dose is delivered by pressing the injection button until it is in its original end position. Clarify the meaning of this statement.
8. There is no indication in the submission that user testing has been performed for this device. The number of steps involved in performing a successful injection with this device could lead to user errors and potential life threatening situations. You should perform a risk analysis to identify the device use tasks that could lead to patient safety issues and then conduct user testing to identify and test mitigation measures that adequately reduce the risk of patient injury. Potential problems such as overdosing, underdosing, or misdosing can result from a variety of user-related tasks such as improper use of the dialing mechanism, failure to properly attach the needle, etc. User testing should be performed to determine and mitigate all potential use-related issues. Without results from usability testing leading to mitigation of hazards and changes in system requirements, it is not possible to determine whether the future marketed device will be safe and effective. Provide a test plan and test results for usability testing for the new device. We recommend that you consult the following guidance documents for information about acceptable usability testing:
  - Do It By Design - An Introduction to Human Factors in Medical Devices <http://www.fda.gov/cdrh/humfac/doitpdf.pdf>
  - Medical Device Use-Safety: Incorporating Human Factors Engineering into Risk Management <http://www.fda.gov/cdrh/humfac/1497.pdf>

**LABELING**

9. In addition, you must submit draft labeling revised as follows:

A. PEN LABEL

- a.  (b) (4)
- b.  (b) (4)
- c.  (b) (4)

B. CARTON LABELING

a. [REDACTED] (b) (4)

b. [REDACTED] (b) (4)

C. PEN DEVICE

a. The Lantus SoloStar device has a purple injection button whereas the Apidra SoloStar device has a “dark blue” injection button. [REDACTED] (b) (4)

b. [REDACTED] (b) (4)

We will provide complete comments on labeling when the deficiencies listed above have been addressed.

If additional information relating to the safety or effectiveness of these drugs becomes available, revision of the labeling may be required.

Within 10 days after the date of this letter, you are required to amend the application, notify us of your intent to file an amendment, or follow one of your other options under 21 CFR 314.110. If you do not follow one of these options, we will consider your lack of response a request to withdraw the applications under 21 CFR 314.65. Any amendment should respond to all the deficiencies listed. We will not process a partial reply as a major amendment nor will the review clock be reactivated until all deficiencies have been addressed.

These products may be considered to be misbranded under the Federal Food, Drug, and Cosmetic Act if they are marketed with these changes before approval of these supplemental applications.

If you have any questions, call Enid Galliers, Supervisory Project Manager, at (301) 796-1211.

Sincerely,

*{See appended electronic signature page}*

Mary H. Parks, M.D.  
Director  
Division of Metabolism and Endocrinology Products  
Office of Drug Evaluation II  
Center for Drug Evaluation and Research

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Mary Parks  
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*APPLICATION NUMBER:*  
**NDA 021629/S-008**

**LABELING**

## HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use APIDRA safely and effectively. See full prescribing information for APIDRA.

**APIDRA (insulin glulisine [rDNA origin] injection) solution for injection**  
**Initial U.S. Approval: 2004**

### RECENT MAJOR CHANGES

Indications and Usage (1) 10/2008

### INDICATIONS AND USAGE

APIDRA is a rapid acting human insulin analog indicated to improve glycemic control in adults and children with diabetes mellitus. (1)

### DOSAGE AND ADMINISTRATION

The dosage of APIDRA must be individualized (2.1)

<b>Subcutaneous Injection</b>	Administer within 15 minutes before a meal or within 20 minutes after starting a meal. Use in a regimen with an intermediate or long-acting insulin. (2.1, 2.2)
<b>Continuous Subcutaneous Infusion Pump</b>	APIDRA must not be mixed or diluted when used in an external insulin infusion pump. (2.3)
<b>Intravenous Infusion</b>	Infuse intravenously (0.05 Units/mL to 1 Units/mL APIDRA in 0.9% sodium chloride using polyvinyl chloride infusion bags) only under strict medical supervision with close monitoring of blood glucose and potassium. (2.4)

### DOSAGE FORMS AND STRENGTHS

APIDRA 100 units/mL (U-100) is available as: (3)

- 10 mL vials
- 3 mL cartridge system for use in OptiClik® (Insulin Delivery Device)
- 3 mL SoloStar® prefilled pen

### CONTRAINDICATIONS

- Do not use during episodes of hypoglycemia (4)
- Do not use in patients with hypersensitivity to APIDRA or any of its excipients (4)

### WARNINGS AND PRECAUTIONS

- Dose adjustment and monitoring: Closely monitor blood glucose in all patients treated with insulin. Change insulin regimens cautiously and only under medical supervision. (5.1)
- Hypoglycemia: Most common adverse reaction of insulin therapy and may be life-threatening (5.2)
- Allergic reactions: Severe, life-threatening, generalized allergy, including anaphylaxis, can occur with any insulin, including APIDRA (5.3)
- Hypokalemia: All insulins, including APIDRA can cause hypokalemia, which if untreated, may result in respiratory paralysis, ventricular arrhythmia, and death (5.4)
- Renal or hepatic impairment: Like all insulins, may require a reduction in the APIDRA dose (5.5)
- Mixing: APIDRA for subcutaneous injection should not be mixed with insulins other than NPH insulin. Do not mix APIDRA with any insulin for intravenous administration or for use in a continuous infusion pump (5.6)
- Pump use: Change the APIDRA in the pump reservoir every 48 hours (5.7)
- Intravenous use: Frequently monitor for hypoglycemia and hypokalemia. (5.8)

### ADVERSE REACTIONS

Adverse reactions commonly associated with APIDRA include hypoglycemia, allergic reactions, injection site reactions, lipodystrophy, pruritus, and rash. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact sanofi-aventis at 1-800-633-1610 or FDA at 1-800-FDA-1088 or [www.fda.gov/medwatch](http://www.fda.gov/medwatch).

### DRUG INTERACTIONS

- Certain drugs affect glucose metabolism and may necessitate insulin dose adjustment (7)
- The signs of hypoglycemia may be reduced or absent in patients taking anti-adrenergic drugs (e.g., beta-blockers, clonidine, guanethidine, and reserpine). (7)

### USE IN SPECIFIC POPULATIONS

- APIDRA has not been studied in children under 4 years of age (8.4)

See 17 for PATIENT COUNSELING INFORMATION

Revised: February 2009

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\*Sections or subsections omitted from the full prescribing information are not listed.

## FULL PRESCRIBING INFORMATION

### 1 INDICATIONS AND USAGE

APIDRA is indicated to improve glycemic control in adults and children with diabetes mellitus.

### 2 DOSAGE AND ADMINISTRATION

#### 2.1 Dosage considerations

APIDRA is a recombinant insulin analog that is equipotent to human insulin (i.e. one unit of APIDRA has the same glucose-lowering effect as one unit of regular human insulin) when given intravenously. When given subcutaneously, APIDRA has a more rapid onset of action and a shorter duration of action than regular human insulin.

The dosage of APIDRA must be individualized. Blood glucose monitoring is essential in all patients receiving insulin therapy.

The total daily insulin requirement may vary and is usually between 0.5 to 1 Unit/kg/day. Insulin requirements may be altered during stress, major illness, or with changes in exercise, meal patterns, or coadministered drugs.

#### 2.2 Subcutaneous administration

APIDRA should be given within 15 minutes before a meal or within 20 minutes after starting a meal.

APIDRA given by subcutaneous injection should generally be used in regimens with an intermediate or long-acting insulin.

APIDRA should be administered by subcutaneous injection in the abdominal wall, thigh, or upper arm. Injection sites should be rotated within the same region (abdomen, thigh or upper arm) from one injection to the next to reduce the risk of lipodystrophy [*See Adverse Reactions (6.1)*].

#### 2.3 Continuous subcutaneous infusion (insulin pump)

APIDRA may be administered by continuous subcutaneous infusion in the abdominal wall. Do not use diluted or mixed insulins in external insulin pumps. Infusion sites should be rotated within the same region to reduce the risk of lipodystrophy [*See Adverse Reactions (6.1)*]. The initial programming of the external insulin infusion pump should be based on the total daily insulin dose of the previous regimen.

The following insulin pumps<sup>†</sup> have been used in APIDRA clinical trials conducted by sanofi-aventis, the manufacturer of APIDRA:

- Disetronic® H-Tron® plus V100 and D-Tron® with Disetronic catheters (Rapid™, Rapid C™, Rapid D™, and Tender™)
- MiniMed® Models 506, 507, 507c and 508 with MiniMed catheters (Sof-set Ultimate QR™, and Quick-set™).

Before using a different insulin pump with APIDRA, read the pump label to make sure the pump has been evaluated with APIDRA.

Physicians and patients should carefully evaluate information on pump use in the APIDRA prescribing information, Patient Information Leaflet, and the pump manufacturer's manual. APIDRA-specific information should be followed for in-use time, frequency of changing infusion sets, or other details specific to APIDRA usage, because APIDRA-specific information may differ from general pump manual instructions.

Based on *in vitro* studies which have shown loss of the preservative, metacresol and insulin degradation, APIDRA in the reservoir should be changed at least every 48 hours. APIDRA in clinical use should not be exposed to temperatures greater than 98.6°F (37°C). [*See Warnings and Precautions (5.7) and How Supplied/Storage and Handling (16.2)*].

## **2.4 Intravenous administration**

APIDRA can be administered intravenously under medical supervision for glycemic control with close monitoring of blood glucose and serum potassium to avoid hypoglycemia and hypokalemia. For intravenous use, APIDRA should be used at concentrations of 0.05 Units/mL to 1 Unit/mL insulin glulisine in infusion systems using polyvinyl chloride (PVC) bags. APIDRA has been shown to be stable only in normal saline solution (0.9% sodium chloride). Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit. Do not administer insulin mixtures intravenously.

## **3 DOSAGE FORMS AND STRENGTHS**

APIDRA 100 units per mL (U-100) is available as:

- 10 mL vials
- 3 mL cartridges for use in the OptiClik<sup>®</sup> Insulin Delivery Device
- 3 mL SoloStar prefilled pen

## **4 CONTRAINDICATIONS**

APIDRA is contraindicated:

- during episodes of hypoglycemia
  - in patients who are hypersensitive to APIDRA or to any of its excipients
- When used in patients with known hypersensitivity to APIDRA or its excipients, patients may develop localized or generalized hypersensitivity reactions [*See Adverse Reactions (6.1)*].

## 5 WARNINGS AND PRECAUTIONS

### 5.1 Dosage adjustment and monitoring

Glucose monitoring is essential for patients receiving insulin therapy. Changes to an insulin regimen should be made cautiously and only under medical supervision. Changes in insulin strength, manufacturer, type, or method of administration may result in the need for a change in insulin dose. Concomitant oral antidiabetic treatment may need to be adjusted.

As with all insulin preparations, the time course of action for APIDRA may vary in different individuals or at different times in the same individual and is dependent on many conditions, including the site of injection, local blood supply, or local temperature. Patients who change their level of physical activity or meal plan may require adjustment of insulin dosages.

### 5.2 Hypoglycemia

Hypoglycemia is the most common adverse reaction of insulin therapy, including APIDRA. The risk of hypoglycemia increases with tighter glycemic control. Patients must be educated to recognize and manage hypoglycemia. Severe hypoglycemia may lead to unconsciousness and/or convulsions and may result in temporary or permanent impairment of brain function or death. Severe hypoglycemia requiring the assistance of another person and/or parenteral glucose infusion or glucagon administration has been observed in clinical trials with insulin, including trials with APIDRA.

The timing of hypoglycemia usually reflects the time-action profile of the administered insulin formulations. Other factors such as changes in food intake (e.g., amount of food or timing of meals), injection site, exercise, and concomitant medications may also alter the risk of hypoglycemia [*See Drug Interactions (7)*].

As with all insulins, use caution in patients with hypoglycemia unawareness and in patients who may be predisposed to hypoglycemia (e.g., the pediatric population and patients who fast or have erratic food intake). The patient's ability to concentrate and react may be impaired as a result of hypoglycemia. This may present a risk in situations where these abilities are especially important, such as driving or operating other machinery.

Rapid changes in serum glucose levels may induce symptoms similar to hypoglycemia in persons with diabetes, regardless of the glucose value. Early warning symptoms of hypoglycemia may be different or less pronounced under certain conditions, such as longstanding diabetes, diabetic nerve disease, use of medications such as beta-blockers [*See Drug Interactions (7)*], or intensified diabetes control. These situations may result in severe hypoglycemia (and, possibly, loss of consciousness) prior to the patient's awareness of hypoglycemia.

Intravenously administered insulin has a more rapid onset of action than subcutaneously administered insulin, requiring closer monitoring for hypoglycemia.

### 5.3 Hypersensitivity and allergic reactions

Severe, life-threatening, generalized allergy, including anaphylaxis, can occur with insulin products, including APIDRA [*See Adverse reactions (6.1)*].

#### **5.4 Hypokalemia**

All insulin products, including APIDRA, cause a shift in potassium from the extracellular to intracellular space, possibly leading to hypokalemia. Untreated hypokalemia may cause respiratory paralysis, ventricular arrhythmia, and death. Use caution in patients who may be at risk for hypokalemia (e.g., patients using potassium-lowering medications, patients taking medications sensitive to serum potassium concentrations). Monitor glucose and potassium frequently when APIDRA is administered intravenously.

#### **5.5 Renal or hepatic impairment**

Frequent glucose monitoring and insulin dose reduction may be required in patients with renal or hepatic impairment [*See Clinical Pharmacology (12.4)*].

#### **5.6 Mixing of insulins**

APIDRA for subcutaneous injection should not be mixed with insulin preparations other than NPH insulin. If APIDRA is mixed with NPH insulin, APIDRA should be drawn into the syringe first. Injection should occur immediately after mixing.

Do not mix APIDRA with other insulins for intravenous administration or for use in a continuous subcutaneous infusion pump.

APIDRA for intravenous administration should not be diluted with solutions other than 0.9% sodium chloride (normal saline). The efficacy and safety of mixing APIDRA with diluents or other insulins for use in external subcutaneous infusion pumps have not been established.

#### **5.7 Subcutaneous insulin infusion pumps**

When used in an external insulin pump for subcutaneous infusion, APIDRA should not be diluted or mixed with any other insulin. APIDRA in the reservoir should be changed at least every 48 hours. APIDRA should not be exposed to temperatures greater than 98.6°F (37°C).

Malfunction of the insulin pump or infusion set or insulin degradation can rapidly lead to hyperglycemia and ketosis. Prompt identification and correction of the cause of hyperglycemia or ketosis is necessary. Interim subcutaneous injections with APIDRA may be required. Patients using continuous subcutaneous insulin infusion pump therapy must be trained to administer insulin by injection and have alternate insulin therapy available in case of pump failure. [*See Dosage and Administration (2.3), How Supplied/Storage and Handling (16), and Patient Counseling Information (17.2)*].

#### **5.8 Intravenous administration**

When APIDRA is administered intravenously, glucose and potassium levels must be closely monitored to avoid potentially fatal hypoglycemia and hypokalemia.

Do not mix APIDRA with other insulins for intravenous administration. APIDRA may be diluted only in normal saline solution.

## 5.9 Drug interactions

Some medications may alter insulin requirements and the risk for hypoglycemia or hyperglycemia [See *Drug Interactions (7)*].

## 6 ADVERSE REACTIONS

The following adverse reactions are discussed elsewhere:

- Hypoglycemia [See *Warnings and Precautions (5.2)*]
- Hypokalemia [See *Warnings and Precautions (5.4)*]

### 6.1 Clinical trial experience

Because clinical trials are conducted under widely varying designs, the adverse reaction rates reported in one clinical trial may not be easily compared to those rates reported in another clinical trial, and may not reflect the rates actually observed in clinical practice.

The frequencies of adverse drug reactions during APIDRA clinical trials in patients with type 1 diabetes mellitus and type 2 diabetes mellitus are listed in the tables below.

**Table 1: Treatment –emergent adverse events in pooled studies of adults with type 1 diabetes (adverse events with frequency  $\geq$  5%)**

	APIDRA, % (n=950)	All comparators <sup>a</sup> , % (n=641)
Nasopharyngitis	10.6	12.9
Hypoglycemia <sup>b</sup>	6.8	6.7
Upper respiratory tract infection	6.6	5.6
Influenza	4.0	5.0

a Insulin lispro, regular human insulin, insulin aspart

b Only severe symptomatic hypoglycemia

**Table 2: Treatment –emergent adverse events in pooled studies of adults with type 2 diabetes (adverse events with frequency  $\geq$  5%)**

	APIDRA, % (n=883)	Regular human insulin, % (n=883)
Upper respiratory tract infection	10.5	7.7
Nasopharyngitis	7.6	8.2
Edema peripheral	7.5	7.8
Influenza	6.2	4.2
Arthralgia	5.9	6.3
Hypertension	3.9	5.3

- *Pediatrics*

Table 3 summarizes the adverse reactions occurring with frequency higher than 5% in a clinical study in children and adolescents with type 1 diabetes treated with APIDRA (n=277) or insulin lispro (n=295).

**Table 3: Treatment –emergent adverse events in children and adolescents with type 1 diabetes (adverse reactions with frequency  $\geq$  5%)**

	APIDRA, % (n=277)	Lispro, % (n=295)
Nasopharyngitis	9.0	9.5
Upper respiratory tract infection	8.3	10.8
Headache	6.9	11.2
Hypoglycemic seizure	6.1	4.7

- *Severe symptomatic hypoglycemia*

Hypoglycemia is the most commonly observed adverse reaction in patients using insulin, including APIDRA [See *Warnings and Precautions (5.2)*]. The rates and incidence of severe symptomatic hypoglycemia, defined as hypoglycemia requiring intervention from a third party, were comparable for all treatment regimens (see Table 4). In the phase 3 clinical trial, children and adolescents with type 1 diabetes had a higher incidence of severe symptomatic hypoglycemia in the two treatment groups compared to adults with type 1 diabetes. (see Table 4) [See *Clinical Studies (14)*].

**Table 4: Severe Symptomatic Hypoglycemia\***

	Type 1 Diabetes Adults 12 weeks with insulin glargine			Type 1 Diabetes Adults 26 weeks with insulin glargine		Type 2 Diabetes Adults 26 weeks with NPH human insulin		Type 1 Diabetes Pediatrics 26 weeks	
	APIDRA Pre-meal	APIDRA Post-meal	Regular Human Insulin	APIDRA	Insulin Lispro	APIDRA	Regular Human Insulin	APIDRA	Insulin Lispro
Events per month per patient	0.05	0.05	0.13	0.02	0.02	0.00	0.00	0.09	0.08
Percent of patients (n/total N)	8.4% (24/286)	8.4% (25/296)	10.1% (28/278)	4.8% (16/339)	4.0% (13/333)	1.4% (6/416)	1.2% (5/420)	16.2% (45/277)	19.3% (57/295)

\* Severe symptomatic hypoglycemia defined as a hypoglycemic event requiring the assistance of another person that met one of the following criteria:

the event was associated with a whole blood referenced blood glucose <36mg/dL or the event was associated with prompt recovery after oral carbohydrate, intravenous glucose or glucagon administration.

- Insulin initiation and intensification of glucose control

Intensification or rapid improvement in glucose control has been associated with a transitory, reversible ophthalmologic refraction disorder, worsening of diabetic retinopathy, and acute painful peripheral neuropathy. However, long-term glycemic control decreases the risk of diabetic retinopathy and neuropathy.

- Lipodystrophy

Long-term use of insulin, including APIDRA, can cause lipodystrophy at the site of repeated insulin injections or infusion. Lipodystrophy includes lipohypertrophy (thickening of adipose tissue) and lipoatrophy (thinning of adipose tissue), and may affect insulin absorption. Rotate insulin injection or infusion sites within the same region to reduce the risk of lipodystrophy. [[See Dosage and Administration \(2.2, 2.3\)](#)].

- Weight gain

Weight gain can occur with insulin therapy, including APIDRA, and has been attributed to the anabolic effects of insulin and the decrease in glucosuria.

- Peripheral Edema

Insulin, including APIDRA, may cause sodium retention and edema, particularly if previously poor metabolic control is improved by intensified insulin therapy.

- Adverse Reactions with Continuous Subcutaneous Insulin Infusion (CSII)

In a 12-week randomized study in patients with type 1 diabetes (n=59), the rates of catheter occlusions and infusion site reactions were similar for APIDRA and insulin aspart treated patients (Table 5).

**Table 5: Catheter Occlusions and Infusion Site Reactions.**

	APIDRA (n=29)	insulin aspart (n=30)
Catheter occlusions/month	0.08	0.15
Infusion site reactions	10.3% (3/29)	13.3% (4/30)

- Allergic Reactions

Local Allergy

As with any insulin therapy, patients taking APIDRA may experience redness, swelling, or itching at the site of injection. These minor reactions usually resolve in a few days to a few weeks, but in some occasions may require discontinuation of APIDRA. In some instances, these reactions may be related to factors other than insulin, such as irritants in a skin cleansing agent or poor injection technique.

Systemic Allergy

Severe, life-threatening, generalized allergy, including anaphylaxis, may occur with any insulin, including APIDRA. Generalized allergy to insulin may cause whole body rash (including pruritus), dyspnea, wheezing, hypotension, tachycardia, or diaphoresis.

In controlled clinical trials up to 12 months duration, potential systemic allergic reactions were reported in 79 of 1833 patients (4.3%) who received APIDRA and 58 of 1524 patients (3.8%) who received the comparator short-acting insulins. During these trials treatment with APIDRA was permanently discontinued in 1 of 1833 patients due to a potential systemic allergic reaction.

Localized reactions and generalized myalgias have been reported with the use of metacresol, which is an excipient of APIDRA.

#### *Antibody Production*

In a study in patients with type 1 diabetes (n=333), the concentrations of insulin antibodies that react with both human insulin and insulin glulisine (cross-reactive insulin antibodies) remained near baseline during the first 6 months of the study in the patients treated with APIDRA. A decrease in antibody concentration was observed during the following 6 months of the study. In a study in patients with type 2 diabetes (n=411), a similar increase in cross-reactive insulin antibody concentration was observed in the patients treated with APIDRA and in the patients treated with human insulin during the first 9 months of the study. Thereafter the concentration of antibodies decreased in the APIDRA patients and remained stable in the human insulin patients. There was no correlation between cross-reactive insulin antibody concentration and changes in HbA1c, insulin doses, or incidence of hypoglycemia. The clinical significance of these antibodies is not known.

APIDRA did not elicit a significant antibody response in a study of children and adolescents with type 1 diabetes.

### **6.2 Postmarketing experience**

The following adverse reactions have been identified during post-approval use of APIDRA. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to estimate reliably their frequency or establish a causal relationship to drug exposure.

Medication errors have been reported in which other insulins, particularly long-acting insulins, have been accidentally administered instead of APIDRA [*See Patient Counseling Information (17)*].

## **7 DRUG INTERACTIONS**

A number of drugs affect glucose metabolism and may necessitate insulin dose adjustment and particularly close monitoring.

Drugs that may increase the blood glucose-lowering effect of insulins including APIDRA, and therefore increase the risk of hypoglycemia, include oral antidiabetic products, pramlintide, ACE

inhibitors, disopyramide, fibrates, fluoxetine, monoamine oxidase inhibitors, propoxyphene, pentoxifylline, salicylates, somatostatin analogs, and sulfonamide antibiotics.

Drugs that may reduce the blood-glucose-lowering effect of APIDRA include corticosteroids, niacin, danazol, diuretics, sympathomimetic agents (e.g., epinephrine, albuterol, terbutaline), glucagon, isoniazid, phenothiazine derivatives, somatropin, thyroid hormones, estrogens, progestogens (e.g., in oral contraceptives), protease inhibitors, and atypical antipsychotics.

Beta-blockers, clonidine, lithium salts, and alcohol may either increase or decrease the blood-glucose-lowering effect of insulin.

Pentamidine may cause hypoglycemia, which may sometimes be followed by hyperglycemia.

The signs of hypoglycemia may be reduced or absent in patients taking anti-adrenergic drugs such as beta-blockers, clonidine, guanethidine, and reserpine.

## **8 USE IN SPECIFIC POPULATIONS**

### **8.1 Pregnancy**

Pregnancy Category C: Reproduction and teratology studies have been performed with insulin glulisine in rats and rabbits using regular human insulin as a comparator. Insulin glulisine was given to female rats throughout pregnancy at subcutaneous doses up to 10 Units/kg once daily (dose resulting in an exposure 2 times the average human dose, based on body surface area comparison) and did not have any remarkable toxic effects on embryo-fetal development.

Insulin glulisine was given to female rabbits throughout pregnancy at subcutaneous doses up to 1.5 Units/kg/day (dose resulting in an exposure 0.5 times the average human dose, based on body surface area comparison). Adverse effects on embryo-fetal development were only seen at maternal toxic dose levels inducing hypoglycemia. Increased incidence of post-implantation losses and skeletal defects were observed at a dose level of 1.5 Units/kg once daily (dose resulting in an exposure 0.5 times the average human dose, based on body surface area comparison) that also caused mortality in dams. A slight increased incidence of post-implantation losses was seen at the next lower dose level of 0.5 Units/kg once daily (dose resulting in an exposure 0.2 times the average human dose, based on body surface area comparison) which was also associated with severe hypoglycemia but there were no defects at that dose. No effects were observed in rabbits at a dose of 0.25 Units/kg once daily (dose resulting in an exposure 0.1 times the average human dose, based on body surface area comparison). The effects of insulin glulisine did not differ from those observed with subcutaneous regular human insulin at the same doses and were attributed to secondary effects of maternal hypoglycemia.

There are no well-controlled clinical studies of the use of APIDRA in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. It is essential for patients with diabetes or a history of gestational diabetes to maintain good metabolic control before conception and throughout pregnancy. Insulin requirements may decrease during

the first trimester, generally increase during the second and third trimesters, and rapidly decline after delivery. Careful monitoring of glucose control is essential in these patients.

### **8.3 Nursing mothers**

It is unknown whether insulin glulisine is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when APIDRA is administered to a nursing woman. Use of APIDRA is compatible with breastfeeding, but women with diabetes who are lactating may require adjustments of their insulin doses.

### **8.4 Pediatric use**

The safety and effectiveness of subcutaneous injections of APIDRA have been established in pediatric patients (age 4 to 17 years) with type 1 diabetes [See *Clinical Studies (14.4)*]. APIDRA has not been studied in pediatric patients with type 1 diabetes younger than 4 years of age and in pediatric patients with type 2 diabetes.

As in adults, the dosage of APIDRA must be individualized in pediatric patients based on metabolic needs and frequent monitoring of blood glucose.

### **8.5 Geriatric use**

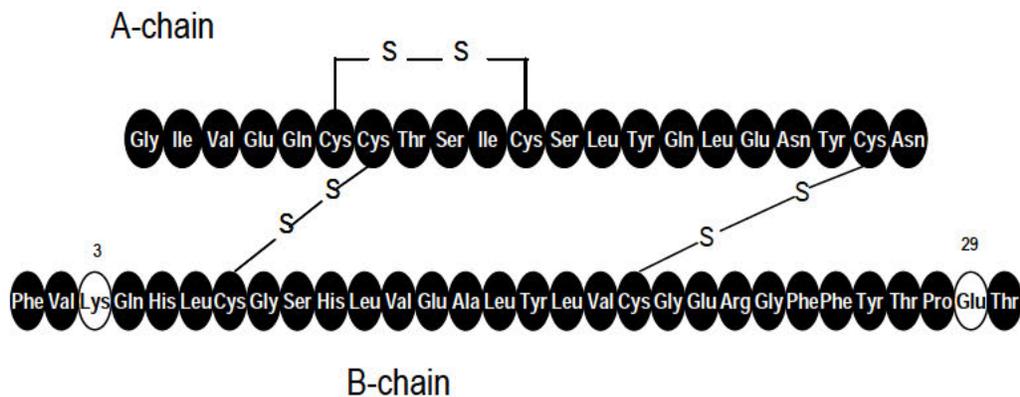
In clinical trials (n=2408), APIDRA was administered to 147 patients  $\geq 65$  years of age and 27 patients  $\geq 75$  years of age. The majority of this small subset of elderly patients had type 2 diabetes. The change in HbA1c values and hypoglycemia frequencies did not differ by age. Nevertheless, caution should be exercised when APIDRA is administered to geriatric patients.

## **10 OVERDOSAGE**

Excess insulin may cause hypoglycemia and, particularly when given intravenously, hypokalemia. Mild episodes of hypoglycemia usually can be treated with oral glucose. Adjustments in drug dosage, meal patterns, or exercise may be needed. More severe episodes of hypoglycemia with coma, seizure, or neurologic impairment may be treated with intramuscular/subcutaneous glucagon or concentrated intravenous glucose. Sustained carbohydrate intake and observation may be necessary because hypoglycemia may recur after apparent clinical recovery. Hypokalemia must be corrected appropriately.

## **11 DESCRIPTION**

APIDRA<sup>®</sup> (insulin glulisine [rDNA origin] injection) is a rapid-acting human insulin analog used to lower blood glucose. Insulin glulisine is produced by recombinant DNA technology utilizing a non-pathogenic laboratory strain of *Escherichia coli* (K12). Insulin glulisine differs from human insulin in that the amino acid asparagine at position B3 is replaced by lysine and the lysine in position B29 is replaced by glutamic acid. Chemically, insulin glulisine is 3<sup>B</sup>-lysine-29<sup>B</sup>-glutamic acid-human insulin, has the empirical formula C<sub>258</sub>H<sub>384</sub>N<sub>64</sub>O<sub>78</sub>S<sub>6</sub> and a molecular weight of 5823 and has the following structural formula:



APIDRA is a sterile, aqueous, clear, and colorless solution. Each milliliter of APIDRA contains 100 units (3.49 mg) insulin glulisine, 3.15 mg metacresol, 6 mg tromethamine, 5 mg sodium chloride, 0.01 mg polysorbate 20, and water for injection. APIDRA has a pH of approximately 7.3. The pH is adjusted by addition of aqueous solutions of hydrochloric acid and/or sodium hydroxide.

## 12 CLINICAL PHARMACOLOGY

### 12.1 Mechanism of action

Regulation of glucose metabolism is the primary activity of insulins and insulin analogs, including insulin glulisine. Insulins lower blood glucose by stimulating peripheral glucose uptake by skeletal muscle and fat, and by inhibiting hepatic glucose production. Insulins inhibit lipolysis and proteolysis, and enhance protein synthesis.

The glucose lowering activities of APIDRA and of regular human insulin are equipotent when administered by the intravenous route. After subcutaneous administration, the effect of APIDRA is more rapid in onset and of shorter duration compared to regular human insulin. [See *Pharmacodynamics (12.2)*].

### 12.2 Pharmacodynamics

Studies in healthy volunteers and patients with diabetes demonstrated that APIDRA has a more rapid onset of action and a shorter duration of activity than regular human insulin when given subcutaneously.

In a study in patients with type 1 diabetes (n= 20), the glucose-lowering profiles of APIDRA and regular human insulin were assessed at various times in relation to a standard meal at a dose of 0.15 Units/kg. (Figure 1.)

The maximum blood glucose excursion ( $\Delta\text{GLU}_{\text{max}}$ ; baseline subtracted glucose concentration) for APIDRA injected 2 minutes before a meal was 65 mg/dL compared to 64 mg/dL for regular human insulin injected 30 minutes before a meal (see Figure 1A), and 84 mg/dL for regular human insulin injected 2 minutes before a meal (see Figure 1B). The maximum blood glucose excursion for APIDRA injected 15 minutes after the start of a meal was 85 mg/dL compared to 84 mg/dL for regular human insulin injected 2 minutes before a meal (see Figure 1C).

**Figure 1.** Serial mean blood glucose collected up to 6 hours following a single dose of APIDRA and regular human insulin. APIDRA given 2 minutes (APIDRA - pre) before the start of a meal compared to regular human insulin given 30 minutes (Regular - 30 min) before start of the meal (Figure 1A) and compared to regular human insulin (Regular - pre) given 2 minutes before a meal (Figure 1B). APIDRA given 15 minutes (APIDRA - post) after start of a meal compared to regular human insulin (Regular - pre) given 2 minutes before a meal (Figure 1C). On the x-axis zero (0) is the start of a 15-minute meal.

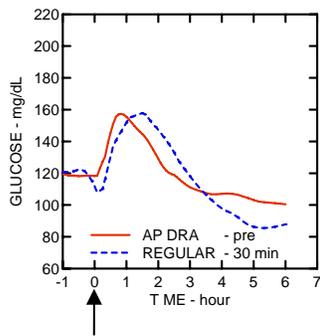


Figure 1A

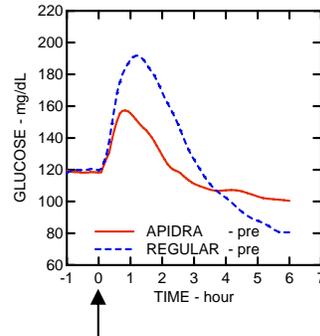


Figure 1B

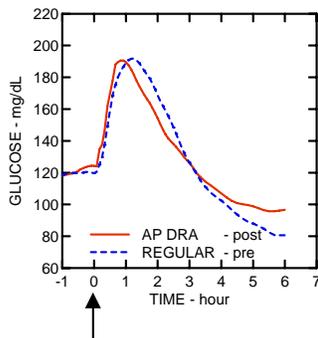


Figure 1C

Arrow ↑ indicates start of a 15-minute meal

In a randomized, open-label, two-way crossover study, 16 healthy male subjects received an intravenous infusion of APIDRA or regular human insulin with saline diluent at a rate of 0.8 milliUnits/kg/min for two hours. Infusion of the same dose of APIDRA or regular human insulin produced equivalent glucose disposal at steady state.

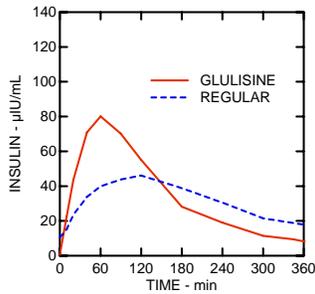
### 12.3 Pharmacokinetics

#### *Absorption and bioavailability*

Pharmacokinetic profiles in healthy volunteers and patients with diabetes (type 1 or type 2) demonstrated that absorption of insulin glulisine was faster than that of regular human insulin.

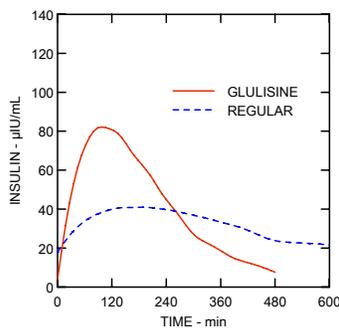
In a study in patients with type 1 diabetes (n=20) after subcutaneous administration of 0.15 Units/kg, the median time to maximum concentration ( $T_{max}$ ) was 60 minutes (range 40 to 120 minutes) and the peak concentration ( $C_{max}$ ) was 83 microUnits/mL (range 40 to 131 microUnits/mL) for insulin glulisine compared to a median  $T_{max}$  of 120 minutes (range 60 to 239 minutes) and a  $C_{max}$  of 50 microUnits/mL (range 35 to 71 microUnits/mL) for regular human insulin. (Figure 2)

**Figure 2.** Pharmacokinetic profiles of insulin glulisine and regular human insulin in patients with type 1 diabetes after a dose of 0.15 Units/kg.



Insulin glulisine and regular human insulin were administered subcutaneously at a dose of 0.2 Units/kg in an euglycemic clamp study in patients with type 2 diabetes (n=24) and a body mass index (BMI) between 20 and 36 kg/m<sup>2</sup>. The median time to maximum concentration ( $T_{max}$ ) was 100 minutes (range 40 to 120 minutes) and the median peak concentration ( $C_{max}$ ) was 84 microUnits/mL (range 53 to 165 microUnits/mL) for insulin glulisine compared to a median  $T_{max}$  of 240 minutes (range 80 to 360 minutes) and a median  $C_{max}$  of 41 microUnits/mL (range 33 to 61 microUnits/mL) for regular human insulin. (Figure 3.)

**Figure 3.** Pharmacokinetic profiles of insulin glulisine and regular human insulin in patients with type 2 diabetes after a subcutaneous dose of 0.2 Units/kg.



When APIDRA was injected subcutaneously into different areas of the body, the time-concentration profiles were similar. The absolute bioavailability of insulin glulisine after subcutaneous administration is approximately 70%, regardless of injection area (abdomen 73%, deltoid 71%, thigh 68%).

In a clinical study in healthy volunteers (n=32) the total insulin glulisine bioavailability was similar after subcutaneous injection of insulin glulisine and NPH insulin (premixed in the syringe) and following separate simultaneous subcutaneous injections. There was 27% attenuation of the maximum concentration ( $C_{\max}$ ) of APIDRA after premixing; however, the time to maximum concentration ( $T_{\max}$ ) was not affected. No data are available on mixing APIDRA with insulin preparations other than NPH insulin. [See *Clinical Studies (14)*].

#### *Distribution and elimination*

The distribution and elimination of insulin glulisine and regular human insulin after intravenous administration are similar with volumes of distribution of 13 and 21 L and half-lives of 13 and 17 minutes, respectively. After subcutaneous administration, insulin glulisine is eliminated more rapidly than regular human insulin with an apparent half-life of 42 minutes compared to 86 minutes.

### **12.4 Clinical pharmacology in specific populations**

#### *Pediatric patients*

The pharmacokinetic and pharmacodynamic properties of APIDRA and regular human insulin were assessed in a study conducted in children 7 to 11 years old (n=10) and adolescents 12 to 16 years old (n=10) with type 1 diabetes. The relative differences in pharmacokinetics and pharmacodynamics between APIDRA and regular human insulin in these patients with type 1 diabetes were similar to those in healthy adult subjects and adults with type 1 diabetes.

#### *Race*

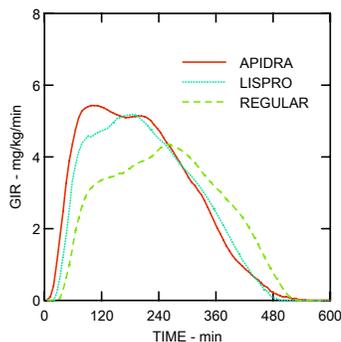
A study in 24 healthy Caucasians and Japanese subjects compared the pharmacokinetics and pharmacodynamics after subcutaneous injection of insulin glulisine, insulin lispro, and regular human insulin. With subcutaneous injection of insulin glulisine, Japanese subjects had a greater initial exposure (33%) for the ratio of  $AUC_{(0-1h)}$  to  $AUC_{(0-clamp\ end)}$  than Caucasians (21%) although the total exposures were similar. There were similar findings with insulin lispro and regular human insulin.

#### *Obesity*

Insulin glulisine and regular human insulin were administered subcutaneously at a dose of 0.3 Units/kg in a euglycemic clamp study in obese, non-diabetic subjects (n=18) with a body mass index (BMI) between 30 and 40 kg/m<sup>2</sup>. The median time to maximum concentration ( $T_{\max}$ ) was 85 minutes (range 49 to 150 minutes) and the median peak concentration ( $C_{\max}$ ) was 192 microUnits/mL (range 98 to 380 microUnits/mL) for insulin glulisine compared to a median  $T_{\max}$  of 150 minutes (range 90 to 240 minutes) and a median  $C_{\max}$  of 86 microUnits/mL (range 43 to 175 microUnits/mL) for regular human insulin.

The more rapid onset of action and shorter duration of activity of APIDRA and insulin lispro compared to regular human insulin were maintained in an obese non-diabetic population (n= 18). (Figure 4.)

**Figure 4.** Glucose infusion rates (GIR) in a euglycemic clamp study after subcutaneous injection of 0.3 Units/kg of APIDRA, insulin lispro or regular human insulin in an obese population.



#### *Renal impairment*

Studies with human insulin have shown increased circulating levels of insulin in patients with renal failure. In a study performed in 24 non-diabetic subjects with normal renal function ( $Cl_{Cr} > 80$  mL/min), moderate renal impairment (30-50 mL/min) and severe renal impairment ( $< 30$  mL/min), the subjects with moderate and severe renal impairment had increased exposure to insulin glulisine by 29% to 40% and reduced clearance of insulin glulisine by 20% to 25% compared to subjects with normal renal function. [*See Warnings and Precautions (5.4)*].

#### *Hepatic impairment*

The effect of hepatic impairment on the pharmacokinetics and pharmacodynamics of APIDRA has not been studied. Some studies with human insulin have shown increased circulating levels of insulin in patients with liver failure. [*See Warnings and Precautions (5.4)*].

#### *Gender*

The effect of gender on the pharmacokinetics and pharmacodynamics of APIDRA has not been studied.

#### *Pregnancy*

The effect of pregnancy on the pharmacokinetics and pharmacodynamics of APIDRA has not been studied.

#### *Smoking*

The effect of smoking on the pharmacokinetics and pharmacodynamics of APIDRA has not been studied.

## **13 NONCLINICAL TOXICOLOGY**

### **13.1 Carcinogenesis, mutagenesis, impairment of fertility**

Standard 2-year carcinogenicity studies in animals have not been performed. In Sprague Dawley rats, a 12-month repeat dose toxicity study was conducted with insulin glulisine at subcutaneous doses of 2.5, 5, 20 or 50 Units/kg twice daily (dose resulting in an exposure 1, 2, 8, and 20 times the average human dose, based on body surface area comparison).

There was a non-dose dependent higher incidence of mammary gland tumors in female rats administered insulin glulisine compared to untreated controls. The incidence of mammary tumors for insulin glulisine and regular human insulin was similar. The relevance of these findings to humans is not known. Insulin glulisine was not mutagenic in the following tests: Ames test, *in vitro* mammalian chromosome aberration test in V79 Chinese hamster cells, and *in vivo* mammalian erythrocyte micronucleus test in rats.

In fertility studies in male and female rats at subcutaneous doses up to 10 Units/kg once daily (dose resulting in an exposure 2 times the average human dose, based on body surface area comparison), no clear adverse effects on male and female fertility, or general reproductive performance of animals were observed.

## **14 CLINICAL STUDIES**

The safety and efficacy of APIDRA was studied in adult patients with type 1 and type 2 diabetes (n =1833) and in children and adolescent patients (4 to 17 years) with type 1 diabetes (n=572). The primary efficacy parameter in these trials was glycemic control, assessed using glycated hemoglobin (GHb reported as HbA<sub>1c</sub> equivalent).

### **14.1 Type 1 Diabetes-Adults**

A 26-week, randomized, open-label, active-controlled, non-inferiority study was conducted in patients with type 1 diabetes to assess the safety and efficacy of APIDRA (n= 339) compared to insulin lispro (n= 333) when administered subcutaneously within 15 minutes before a meal. Insulin glargine was administered once daily in the evening as the basal insulin. There was a 4-week run-in period with insulin lispro and insulin glargine prior to randomization. Most patients were Caucasian (97%). Fifty eight percent of the patients were men. The mean age was 39 years (range 18 to 74 years). Glycemic control, the number of daily short-acting insulin injections and the total daily doses of APIDRA and insulin lispro were similar in the two treatment groups (Table 6).

**Table 6: Type 1 Diabetes Mellitus–Adult**

Treatment duration Treatment in combination with:	26 weeks Insulin glargine	
	<u>APIDRA</u>	<u>Insulin Lispro</u>
Glycated hemoglobin (GHb)* (%)		
Number of patients	331	322
Baseline mean	7.6	7.6
Adjusted mean change from baseline	-0.1	-0.1
Treatment difference: APIDRA – Insulin Lispro	0.0	
95% CI for treatment difference	(-0.1; 0.1)	
Basal insulin dose (Units/day)		
Baseline mean	24	24
Adjusted mean change from baseline	0	2
Short-acting insulin dose (Units/day)		
Baseline mean	30	31
Adjusted mean change from baseline	-1	-1
Mean number of short-acting insulin injections per day	3	3
Body weight (kg)		
Baseline mean	73.9	74.1
Mean change from baseline	0.6	0.3

\*GHb reported as HbA<sub>1c</sub> equivalent

## 14.2 Type 2 Diabetes-Adults

A 26-week, randomized, open-label, active-controlled, non-inferiority study was conducted in insulin-treated patients with type 2 diabetes to assess the safety and efficacy of APIDRA (n=435) given within 15 minutes before a meal compared to regular human insulin (n=441) administered 30 to 45 minutes prior to a meal. NPH human insulin was given twice a day as the basal insulin. All patients participated in a 4-week run-in period with regular human insulin and NPH human insulin. Eighty-five percent of patients were Caucasian and 11% were Black. The mean age was 58 years (range 26 to 84 years). The average body mass index (BMI) was 34.6 kg/m<sup>2</sup>. At randomization, 58% of the patients were taking an oral antidiabetic agent. These patients were instructed to continue use of their oral antidiabetic agent at the same dose throughout the trial. The majority of patients (79%) mixed their short-acting insulin with NPH human insulin immediately prior to injection. The reductions from baseline in GHb were similar between the 2 treatment groups (see Table 7). No differences between APIDRA and regular human insulin groups were seen in the number of daily short-acting insulin injections or basal or short-acting insulin doses. (See Table 7.)

**Table 7: Type 2 Diabetes Mellitus–Adult**

Treatment duration Treatment in combination with:	26 weeks NPH human insulin	
	<u>APIDRA</u>	<u>Regular Human Insulin</u>
Glycated hemoglobin (GHb)* (%)		
Number of patients	404	403
Baseline mean	7.6	7.5
Adjusted mean change from baseline	-0.5	-0.3
Treatment difference: APIDRA – Regular Human Insulin		-0.2
95% CI for treatment difference		(-0.3; -0.1)
Basal insulin dose (Units/day)		
Baseline mean	59	57
Adjusted mean change from baseline	6	6
Short-acting insulin dose (Units/day)		
Baseline mean	32	31
Adjusted mean change from baseline	4	5
Mean number of short-acting insulin injections per day	2	2
Body weight (kg)		
Baseline mean	100.5	99.2
Mean change from baseline	1.8	2.0

\*GHb reported as HbA<sub>1c</sub> equivalent

### 14.3 Type 1 Diabetes-Adults: Pre- and post-meal administration

A 12-week, randomized, open-label, active-controlled, non-inferiority study was conducted in patients with type 1 diabetes to assess the safety and efficacy of APIDRA administered at different times with respect to a meal. APIDRA was administered subcutaneously either within 15 minutes before a meal (n=286) or immediately after a meal (n=296) and regular human insulin (n= 278) was administered subcutaneously 30 to 45 minutes prior to a meal. Insulin glargine was administered once daily at bedtime as the basal insulin. There was a 4-week run-in period with regular human insulin and insulin glargine followed by randomization. Most patients were Caucasian (94%). The mean age was 40 years (range 18 to 73 years). Glycemic control (see Table 8) was comparable for the 3 treatment regimens. No changes from baseline between the treatments were seen in the total daily number of short-acting insulin injections. (See Table 8.)

**Table 8: Pre- and Post-Meal Administration in Type 1 Diabetes Mellitus–Adult**

Treatment duration	12 weeks	12 weeks	12 weeks
Treatment in combination with:	insulin glargine	insulin glargine	insulin glargine
	<u>APIDRA</u>	<u>APIDRA</u>	<u>Regular Human</u>
	<u>pre meal</u>	<u>post meal</u>	<u>Insulin</u>
Glycated hemoglobin (GHb)* (%)			
Number of patients	268	276	257
Baseline mean	7.7	7.7	7.6
Adjusted mean change from baseline**	-0.3	-0.1	-0.1
Basal insulin dose (Units/day)			
Baseline mean	29	29	28
Adjusted mean change from baseline	1	0	1
Short-acting insulin dose (Units/day)			
Baseline mean	29	29	27
Adjusted mean change from baseline	-1	-1	2
Mean number of short-acting insulin injections per day	3	3	3
Body weight (kg)			
Baseline mean	79.2	80.3	78.9
Mean change from baseline	0.3	-0.3	0.3

\*GHb reported as HbA<sub>1c</sub> equivalent

\*\*Adjusted mean change from baseline treatment difference (98.33% CI for treatment difference):

APIDRA pre meal vs. Regular Human Insulin - 0.1 (-0.3; 0.0)

APIDRA post meal vs. Regular Human Insulin 0.0 (-0.1; 0.2)

APIDRA post meal vs. pre meal 0.2 (0.0; 0.3)

#### 14.4 Type 1 Diabetes-Pediatric patients

A 26-week, randomized, open-label, active-controlled, non-inferiority study was conducted in children and adolescents older than 4 years of age with type 1 diabetes mellitus to assess the safety and efficacy of APIDRA (n= 277) compared to insulin lispro (n= 295) when administered subcutaneously within 15 minutes before a meal. Patients also received insulin glargine (administered once daily in the evening) or NPH insulin (administered once in the morning and once in the evening). There was a 4-week run-in period with insulin lispro and insulin glargine or NPH prior to randomization. Most patients were Caucasian (91%). Fifty percent of the patients were male. The mean age was 12.5 years (range 4 to 17 years). Mean BMI was 20.6 kg/m<sup>2</sup>. Glycemic control (see Table 9) was comparable for the two treatment regimens.

**Table 9: Results from a 26-week study in pediatric patients with type 1 diabetes mellitus**

	APIDRA	Lispro
Number of patients	271	291
Basal Insulin	NPH or insulin glargine	NPH or insulin glargine
Glycated hemoglobin (GHb)* (%)		
Baseline mean	8.2	8.2
Adjusted mean change from baseline	0.1	0.2
Treatment Difference: Mean (95% confidence interval)	-0.1 (-0.2, 0.1)	
Basal insulin dose (Units/kg/day)		
Baseline mean	0.5	0.5
Mean change from baseline	0.0	0.0
Short-acting insulin dose (Units/kg/day)		
Baseline mean	0.5	0.5
Mean change from baseline	0.0	0.0
Mean number of short-acting insulin injections per day	3	3
Baseline mean body weight (kg)	51.5	50.8
Mean weight change from baseline (kg)	2.2	2.2

\*GHb reported as HbA<sub>1c</sub> equivalent

#### 14.5 Type 1 Diabetes-Adults: Continuous subcutaneous insulin infusion

A 12-week randomized, active control study (APIDRA versus insulin aspart) conducted in adults with type 1 diabetes (APIDRA n= 29, insulin aspart n=30) evaluated the use of APIDRA in an external continuous subcutaneous insulin pump. All patients were Caucasian. The mean age was 46 years (range 21 to 73 years). The mean GHb increased from baseline to endpoint in both treatment groups (from 6.8% to 7.0% for APIDRA; from 7.1% to 7.2% for insulin aspart).

## 16 HOW SUPPLIED/STORAGE AND HANDLING

### 16.1 How supplied

APIDRA 100 units per mL (U-100) is available as:

10 mL vials	NDC 0088-2500-33
3 mL cartridge system*, package of 5	NDC 0088-2500-52
3 mL SoloStar prefilled pen, package of 5	NDC 0088-2502-05

\* Cartridge systems are for use only in OptiClik<sup>®</sup> (Insulin Delivery Device)

Pen needles are not included in the packs.

BD Ultra-Fine<sup>™</sup> pen needles<sup>†</sup> to be used in conjunction with OptiClik are sold separately and are manufactured by Becton Dickinson and Company.

Solostar is compatible with all pen needles from Becton Dickinson and Company, Ypsomed and Owen Mumford.

## 16.2 Storage

Do not use after the expiration date (see carton and container).

### **Unopened Vial/Cartridge System/SoloStar**

Unopened APIDRA vials, cartridge systems and SoloStar should be stored in a refrigerator, 36°F-46°F (2°C-8°C). Protect from light. APIDRA should not be stored in the freezer and it should not be allowed to freeze. Discard if it has been frozen.

Unopened vials/cartridge systems/SoloStar not stored in a refrigerator must be used within 28 days.

### **Open (In-Use) Vial:**

Opened vials, whether or not refrigerated, must be used within 28 days. If refrigeration is not possible, the open vial in use can be kept unrefrigerated for up to 28 days away from direct heat and light, as long as the temperature is not greater than 77°F (25°C).

### **Open (In-Use) Cartridge System:**

The opened (in-use) cartridge system inserted in OptiClik<sup>®</sup> should NOT be refrigerated but should be kept below 77°F (25°C) away from direct heat and light. The opened (in-use) cartridge system must be discarded after 28 days. Do not store OptiClik<sup>®</sup>, with or without cartridge system, in a refrigerator at any time.

### **Open (In-Use) SoloStar prefilled pen:**

The opened (in-use) SoloStar should NOT be refrigerated but should be kept below 77°F (25°C) away from direct heat and light. The opened (in-use) SoloStar kept at room temperature must be discarded after 28 days.

### **Infusion sets:**

Infusion sets (reservoirs, tubing, and catheters) and the APIDRA in the reservoir should be discarded after 48 hours of use or after exposure to temperatures that exceed 98.6°F (37°C).

### **Intravenous use:**

Infusion bags prepared as indicated under [DOSAGE AND ADMINISTRATION \(2.4\)](#) are stable at room temperature for 48 hours.

## 16.3 Preparation and handling

After dilution for intravenous use, the solution should be inspected visually for particulate matter and discoloration prior to administration. Do not use the solution if it has become cloudy or contains particles; use only if it is clear and colorless. APIDRA is not compatible with Dextrose solution and Ringers solution and, therefore, cannot be used with these solution fluids. The use of APIDRA with other solutions has not been studied and is, therefore, not recommended.

Cartridge system: If OptiClik<sup>®</sup> (the Insulin Delivery Device for APIDRA) malfunctions, APIDRA may be drawn from the cartridge system into a U-100 syringe and injected.

## 17 PATIENT COUNSELING INFORMATION

*See FDA-approved patient labeling.*

### 17.1 Instructions for all patients

Patients should be instructed on self-management procedures including glucose monitoring, proper injection technique, and management of hypoglycemia and hyperglycemia.

Patients must be instructed on handling of special situations such as intercurrent conditions (illness, stress, or emotional disturbances), an inadequate or skipped insulin dose, inadvertent administration of an increased insulin dose, inadequate food intake, and skipped meals. Refer patients to the APIDRA Patient Information Leaflet for additional information.

Women with diabetes should be advised to inform their doctor if they are pregnant or are contemplating pregnancy.

Accidental mix-ups between APIDRA and other insulins, particularly long-acting insulins, have been reported. To avoid medication errors between APIDRA and other insulins, patients should be instructed to always check the insulin label before each injection.

### 17.2 For patients using continuous subcutaneous insulin pumps

Patients using external pump infusion therapy should be trained appropriately.

The following insulin pumps<sup>†</sup> have been used in APIDRA clinical trials conducted by sanofi-aventis, the manufacturer of APIDRA:

- Disetronic® H-Tron® plus V100 and D-Tron® with Disetronic catheters (Rapid™, Rapid C™, Rapid D™, and Tender™)
- MiniMed® Models 506, 507, 507c and 508 with MiniMed catheters (Sof-set Ultimate QR™, and Quick-set™).

Before using a different insulin pump with APIDRA, read the pump label to make sure the pump has been evaluated with APIDRA.

To minimize insulin degradation, infusion set occlusion, and loss of the preservative (metacresol), the infusion sets (reservoir, tubing, and catheter) and the APIDRA in the reservoir should be replaced every 48 hours and a new infusion site should be selected. The temperature of the insulin may exceed ambient temperature when the pump housing, cover, tubing or sport case is exposed to sunlight or radiant heat. Insulin exposed to temperatures higher than 98.6°F (37°C) should be discarded. Infusion sites that are erythematous, pruritic, or thickened should be reported to the healthcare professional, and a new site selected because continued infusion may increase the skin reaction or alter the absorption of APIDRA.

Pump or infusion set malfunctions or insulin degradation can lead to rapid hyperglycemia and ketosis. This is especially pertinent for rapid-acting insulin analogs that are more rapidly absorbed through skin and have a shorter duration of action. Prompt identification and correction of the cause of hyperglycemia or ketosis is necessary. Problems include pump malfunction, infusion set occlusion, leakage, disconnection or kinking, and degraded insulin. Less commonly,

hypoglycemia from pump malfunction may occur. If these problems cannot be promptly corrected, patients should resume therapy with subcutaneous insulin injection and contact their healthcare professional. [*See Dosage and Administration (2.3), Warnings and Precautions (5.7), and How Supplied/Storage and Handling (16)*].

sanofi-aventis U.S. LLC  
Bridgewater, NJ 08807

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## **Patient Information**

### **APIDRA (uh PEE druh) (insulin glulisine [recombinant DNA origin] injection) solution for injection**

Read the Patient Information that comes with APIDRA before you start taking 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 diabetes or treatment. If you have questions about APIDRA or about diabetes, talk with your healthcare provider.

#### **What is APIDRA?**

APIDRA is a man-made insulin used to control high blood sugar in adults and children with diabetes mellitus.

It is not known if APIDRA is safe or effective in:

- children under age 4 with type 1 diabetes
- children with type 2 diabetes

#### **Who should NOT take APIDRA?**

##### **Do not take APIDRA:**

- when your blood sugar is too low (hypoglycemia). See the section, “What are the possible side effects of APIDRA?”
- if you are allergic to any of the ingredients in APIDRA. See the end of this leaflet for a complete list of ingredients. Ask your healthcare provider if you are not sure.

#### **What should I tell my healthcare provider before taking APIDRA?**

**Medical conditions can affect your insulin needs. Tell your healthcare provider about all of your medical conditions, including if you:**

- **have liver or kidney problems.**
- **are pregnant, plan to become pregnant, or are breast-feeding.** It is not known if APIDRA will harm your unborn baby or nursing child. You and your healthcare provider should talk about the best way to manage your diabetes while you are pregnant or breast-feeding. It is especially important to keep good control of your blood sugar during pregnancy.

**Tell your healthcare provider about all the medicines you take, including prescription and non-prescription medicines, vitamins, and herbal supplements.**

Know the medicines you take. Keep a list of your medicines with you and show it to your healthcare provider and pharmacist when you get a new medicine.

### **How should I take APIDRA?**

- Take APIDRA exactly as prescribed.
- Do not make any changes to your dose or type of insulin unless told to do so by your healthcare provider.
- Know your insulin. Make sure you know:
  - the type and strength of insulin prescribed for you
  - the amount of insulin you take
  - the best time for you to take your insulin. This may change if you take a different type of insulin or if the way you give your insulin changes for example, using an insulin pump instead of giving injections under the skin (subcutaneous injections).
- APIDRA starts working faster than regular insulin, but does not work as long.
- APIDRA is usually used with a longer-acting insulin when given by injection under the skin (subcutaneous), or by itself when using an insulin pump.
- **Read the instructions for use that come with your APIDRA.** Talk to your healthcare provider if you have any questions. Your healthcare provider should show you how to inject APIDRA before you start taking it.
- Your healthcare provider will prescribe the best type of APIDRA for you. APIDRA is available in:
  - 3 mL cartridge system for use in OptiClik<sup>®</sup> Insulin Delivery Device
  - 3 mL SoloStar<sup>®</sup> prefilled pen
  - 10 mL vials

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

- Check your blood sugar level before each use of APIDRA. Ask your healthcare provider what your blood sugars should be and when you should check your blood sugar levels.
- Check the label to make sure you have the correct insulin type. This is especially important if you also take long-acting insulin.
- APIDRA should look clear and colorless. Do not use APIDRA if it looks cloudy, colored, or has particles in it. Talk with your pharmacist or healthcare provider if you have any questions.
- If you take too much APIDRA, your blood sugar may fall low (hypoglycemia). You can treat mild low blood sugar (hypoglycemia) by drinking or eating something sugary right away.
- **Do not share needles, insulin pens or syringes with others.**

**Your dose of APIDRA may need to be changed because of:**

- illness
- stress
- other medicines you take
- change in diet
- change in physical activity or exercise
- travel

Check your blood sugar and stay on the diet and exercise plan as prescribed by your healthcare provider.

### **What should I consider while taking APIDRA?**

- Alcohol may affect your blood sugar when you take APIDRA
- **Driving and operating machinery.** You may have trouble paying attention or reacting if you have low blood sugar (hypoglycemia). Be careful when you drive a car or operate machinery. Ask your healthcare provider if it is alright for you to drive if you have:
  - low blood sugar (hypoglycemia)
  - decreased or no warning signs of low blood sugar

### **What are the possible side effects of APIDRA?**

APIDRA can cause serious side effects, including:

- **Low blood sugar (hypoglycemia).** Symptoms of low blood sugar may include:
  - feeling anxious, or irritable, mood changes
  - trouble concentrating or feeling confused
  - tingling in your hands, feet, lips, or tongue
  - feeling dizzy, light-headed, or drowsy
  - nightmares or trouble sleeping
  - headache
  - blurred vision
  - slurred speech
  - a fast heart beat
  - sweating
  - shakiness
  - walking unsteady

Very low blood sugar (hypoglycemia) can cause unconsciousness (passing out), seizures, and death. Talk to your healthcare provider about how to tell if you have low blood sugar and what to do if this happens while taking APIDRA. Know your symptoms of low blood sugar. Follow your healthcare provider's instructions for treating your low blood sugar.

Talk to your healthcare provider if low blood sugar is a problem for you. Your dose of APIDRA may need to be changed.

- **Serious allergic reactions.**

Get medical help right away if you have any of these symptoms of a severe allergic reaction:

- a rash all over your body
- shortness of breath
- trouble breathing (wheezing)
- fast pulse
- sweating
- feel faint (due to low blood pressure)

- **Low potassium** in your blood. Your doctor will check you for this.

Common side effects include:

- **Reactions at the injection site** (local allergic reaction). You may get redness, swelling and itching at the injection site. If you keep having skin reactions or they are serious talk to your healthcare provider.
- **Skin thickening or pits at the injection site.** Do not inject insulin into skin where this has happened. Choose an injection area (upper arm, thigh, or stomach area). Change injection sites within the area you choose with each dose. **Do not inject into the exact same spot for each injection.**
- Weight gain

Tell your healthcare provider about any side effect that bothers you or that does not go away. These are not all of the possible side effects of APIDRA.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-332-1088.

### **How should I store APIDRA?**

- See the Patient Instructions for Use that come with your APIDRA for specific storage instructions.

### **Unopened APIDRA:**

- Do not use APIDRA after the expiration date stamped on the label.
- Keep all unopened APIDRA in the refrigerator between 36°F to 46°F (2°C to 8°C).
- Do not freeze. Do not use APIDRA if it has been frozen.
- Keep APIDRA away from direct heat and light.
- Unopened vials, cartridge systems and SoloStar that were not kept in a refrigerator must be used within 28 days after opening.

### **General Information about APIDRA**

Medicines are sometimes prescribed for conditions that are not mentioned in patient information leaflets. Do not use APIDRA for a condition for which it was not prescribed. Do not give APIDRA to other people, even if they have the same symptoms you have. It may harm them.

This leaflet summarizes the most important information about APIDRA. If you would like more information, talk with your healthcare provider. You can ask your healthcare provider for information about APIDRA that is written for healthcare providers. For more information about APIDRA call 1-800-633-1610 or go to [www.apidra.com](http://www.apidra.com).

### **What are the ingredients in APIDRA?**

Active ingredient: insulin glulisine

Inactive ingredients: metacresol, tromethamine, sodium chloride, polysorbate 20, water for injection, hydrochloric acid or sodium hydroxide

### **ADDITIONAL INFORMATION**

**DIABETES FORECAST** is a national magazine designed especially for patients with diabetes and their families and is available by subscription from the American Diabetes Association, (ADA), P.O. Box 363, Mt. Morris, IL 61054-0363, 1-800-DIABETES (1-800-342-2383). You may also visit the ADA website at [www.diabetes.org](http://www.diabetes.org).

Another publication, **COUNTDOWN**, is available from the Juvenile Diabetes Research Foundation International (JDRF), 120 Wall Street, 19th Floor, New York, New York 10005, 1-800-JDF-CURE (1-800-533-2873). You may also visit the JDRF website at [www.jdf.org](http://www.jdf.org). To get more information about diabetes, check with your healthcare provider or diabetes educator or visit [www.DiabetesWatch.com](http://www.DiabetesWatch.com).

For more information about APIDRA or OptiClik<sup>®</sup> call 1-800-633-1610 or visit [www.apidra.com](http://www.apidra.com) or [www.opticlik.com](http://www.opticlik.com).

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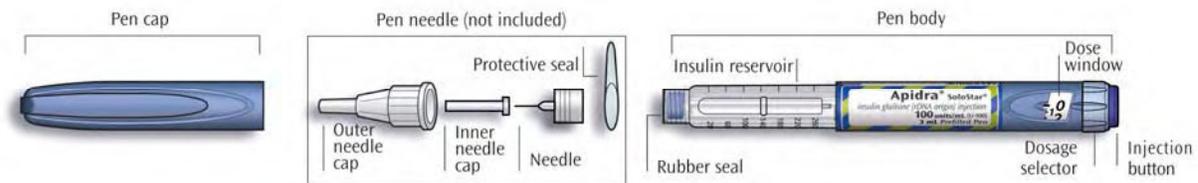
**APIDRA® SoloStar®**  
(insulin glulisine [rDNA origin] injection)  
3 mL prefilled pen

**Patient Instructions for Use**

Be sure that you read, understand and follow these instructions before you use your APIDRA SoloStar®. Talk with your healthcare provider about the right way to use your APIDRA SoloStar before you use it for the first time. Keep this leaflet in case you need to look at it again later.

APIDRA SoloStar should not be used by people who are blind or have severe vision problems, without the help of a person who has good eyesight and who is trained to use the APIDRA SoloStar the right way.

APIDRA SoloStar is a disposable prefilled pen used to inject APIDRA. Each APIDRA SoloStar has 300 units of insulin which can be used for many doses. You can select a dose from 1 to 80 units. The pen plunger moves with each dose. The plunger will only move to the end of the cartridge when 300 units of insulin have been given.



If you will give yourself subcutaneous injections of APIDRA:

- You should take APIDRA within 15 minutes before a meal or within 20 minutes after starting a meal.
- Do not inject APIDRA if you are not going to eat within 15 minutes.
- Inject APIDRA into the skin of your upper arm, thigh, or stomach area. Do not inject APIDRA into a vein or into a muscle.
- Choose an injection area (upper arm, thigh, or stomach area). Change injection sites within the area you choose with each dose. **Do not inject into the exact same spot for each injection.**

**Important information for use of APIDRA SoloStar:**

- Use a new needle for each injection.  
APIDRA Solostar may be used with pen needles from Becton Dickinson and Company, Ypsomed and Owen Mumford. Contact your healthcare provider for further information.
- Do a safety test before each injection. (See step 3.)
- Do not share your APIDRA SoloStar with others even if they have diabetes.

- If your injection is given by another person, this person must be careful to avoid accidental needle stick injury and prevent passing (transmission of) infection.
- Do not use APIDRA SoloStar if it is damaged or if you are not sure that it is working correctly.
- Always carry an extra APIDRA SoloStar prefilled pen in case your APIDRA SoloStar is lost or damaged.

## **Step 1. Preparing for an injection**

### **Make sure you have the following items:**

- Apidra SoloStar
  - Pen needles
  - Alcohol swab
  - Puncture resistant container. See [“How do I dispose of used needles and APIDRA SoloStar?”](#).
- A.** Check the label on your APIDRA SoloStar to make sure you have the right insulin. The APIDRA Solostar is blue. It has a dark blue injection button with a raised ring on the top.
- B.** Check the expiration date, located on the carton or the label of your APIDRA SoloStar, to make sure the date has not passed. Do not use an APIDRA SoloStar if the date has passed.
- C.** Take off the pen cap.
- D.** Look at the insulin in your APIDRA SoloStar. Check to make sure that the insulin looks clear. Do not use this APIDRA SoloStar if the insulin is cloudy, colored, or has particles in it.

## **Step 2. Attaching the needle**

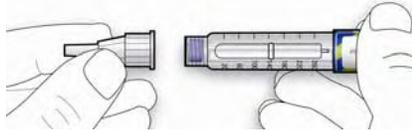
Always use a new sterile needle for each injection to help prevent contamination, and potential needle blocks.

Read the pen needle “Instructions for Use” before you use them.

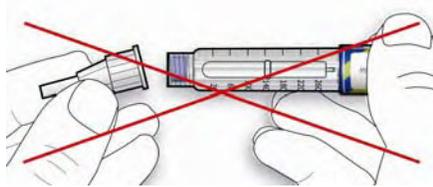
Please note: Pen needles may look different. The pen needles shown are for illustrative purposes only.

- A.** Wipe the Rubber Seal with alcohol.
- B.** Remove the protective seal from the new pen needle.

C. Line up the needle with the pen, and keep it straight as you attach it (screw or push on, depending on the needle type).



- If you do not keep the needle straight while you attach it this can damage the rubber seal, and cause leakage of insulin, or break the needle.

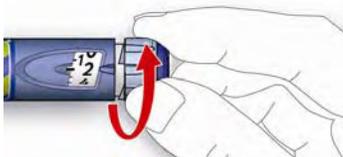


### Step 3. Doing a Safety test

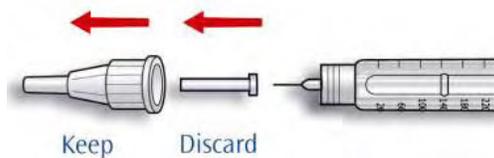
Do a safety test before each injection to make sure that you get the correct dose of APIDRA. The safety test:

- makes sure that the pen and needle work properly
- removes air bubbles

A. Select a dose of 2 units by turning the dosage selector.



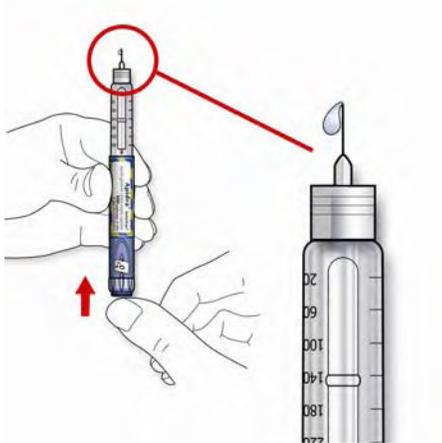
B. Take off the outer needle cap and keep it to remove the used needle after injection. Take off the inner needle cap and dispose of it.



C. Hold the pen with the needle pointing upwards.

D. Tap the insulin reservoir so that any air bubbles rise up towards the needle.

E. Press the injection button all the way in. Check if insulin comes out of the needle tip.



You may have to do the safety test more than once before you see the insulin.

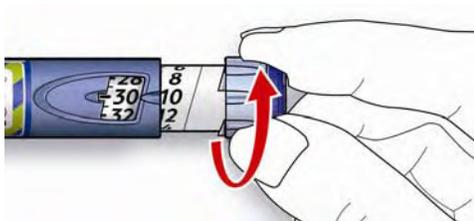
- If no insulin comes out, check for air bubbles and repeat the safety test two more times to remove them.
- If still no insulin comes out, the needle may be blocked. Change the needle and try again.
- If no insulin comes out after changing the needle, your APIDRA SoloStar may be damaged. Do not use this APIDRA SoloStar.

#### Step 4. Selecting your dose

Select the APIDRA dose prescribed by your healthcare provider. You can select the insulin dose in steps of 1 unit, from a minimum of 1 unit to a maximum of 80 units. If you need a dose larger than 80 units, you should give it as two or more injections.

A. Check that the dose window shows “0” after the safety test.

B. Select your needed dose (in the example below, the selected dose is 30 units). If you turn past your dose, you can turn back down.

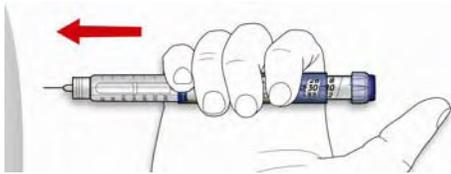


- Do not push the injection button while turning, insulin will come out.

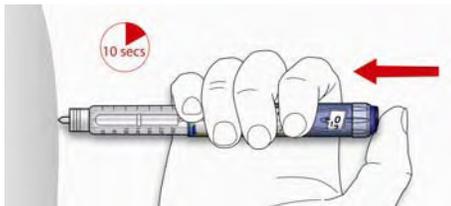
- You cannot turn the dosage selector passed the number of units left in the pen. Do not force the dosage selector to turn. In this case, either you can inject the amount of insulin that is still in the pen and finish your dose with a new APIDRA SoloStar or you can use a new APIDRA SoloStar for your full dose.

## Step 5. Giving the injection

- Give the injection exactly as shown to you by your healthcare provider.
- Insert the needle into your skin.



- Inject the dose by pressing the injection button in all the way. Only push the injection button when you are ready to inject. The number in the dose window will return to “0” as you inject.



- Keep the injection button pressed all the way in. Slowly count to 10 before you take the needle out of your skin. This will make sure that the full dose has been given.

## Step 6. Removing and disposing of the pen needle

Always remove the pen needle after each injection and store your APIDRA SoloStar without a needle attached. This helps prevent:

- Contamination and infection
- Air from getting into the insulin reservoir and leakage of insulin. This will help to make sure you inject the right dose of insulin.

- Follow the instructions from your healthcare provider when removing and disposing of the needle. For example “scoop” the outer needle cap back on the needle and use it to unscrew the used needle from the pen. To lessen the risk of accidental needle stick injury and passing infection:

- do not recap needles with your fingers

- never replace the inner needle cap.

If your injection is given by another person, this person must also be careful when removing and disposing of the needles to prevent accidental needle stick injury and passing infection.

- B.** Dispose of the needle the right way into your special puncture resistant container (See “How Do I Dispose of used needles and APIDRA SoloStar?”).
- C.** Always put the pen cap back on the pen, then store the APIDRA SoloStar until your next injection.

### **How do I dispose of used needles and APIDRA SoloStar?**

- Check with your healthcare provider for instructions about the right way to dispose of used needles and APIDRA SoloStar s. There may be local or state laws about how to throw away used needles and APIDRA SoloStar. Do not dispose of used needles or APIDRA SoloStar in household trash and do not recycle them.
- Put used needles and used empty APIDRA SoloStar in a container made specially for disposing of used syringes and needles (called a “sharps” container) or a hard plastic container (such as empty detergent bottles), with a screw-on cap, or metal container with a plastic lid labeled “Used Syringes”. These containers should be sealed and disposed of the right way.

### **How should I Store APIDRA SoloStar?**

- Do not refrigerate APIDRA SoloStar after first use.
- Keep at room temperature below 77°F (25°C).
- Dispose of any opened APIDRA SoloStar 28 days after first use.

### **Maintenance**

- Protect your APIDRA SoloStar from dust and dirt.
- You can clean the outside of your APIDRA SoloStar by wiping it with a damp cloth.
- Do not soak, wash or lubricate the pen as this may damage it.
- Handle your APIDRA SoloStar with care. Avoid situations where your APIDRA SoloStar might be damaged. If you are concerned that your APIDRA SoloStar may be damaged, use a new one.

If you have any questions about APIDRA SoloStar or about diabetes, ask your healthcare provider, go to [www.apidra.com](http://www.apidra.com) or call sanofi-aventis U.S. at 1-800-633-1610.

sanofi-aventis U.S. LLC  
Bridgewater, NJ 08807

**Date of revision:**

February 2009

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## **PATIENT INSTRUCTIONS FOR USE**

### **APIDRA 3 mL cartridge system (100 Units/mL)**

Be sure to read, understand, and follow these instructions before using your APIDRA<sup>®</sup> 3 mL cartridge system. **Also read and follow the step-by-step instructions in the “OptiClik<sup>®</sup> Instructions for Use Leaflet” that comes with OptiClik. If you do not follow the instructions, you may take too much or too little insulin.** Your healthcare provider should show you how to use the APIDRA 3 mL cartridge system and OptiClik to inject APIDRA before you use it for the first time. Ask your healthcare provider if you have any questions.

### **Important Information**

If you will give yourself subcutaneous injections of APIDRA:

- You should take APIDRA within 15 minutes before a meal or within 20 minutes after starting a meal.
- Do not inject APIDRA if you are not going to eat within 15 minutes.
- Inject APIDRA into the skin of your upper arm, stomach area, or thigh. Do not inject APIDRA into a vein or into a muscle.
- Choose an injection area (upper arm, thigh, or stomach area). Change injection sites within the area you choose with each dose. Do not inject into the exact same spot for each injection.
- Only use your APIDRA 3 mL cartridge system with OptiClik, a reusable insulin delivery device.
- Use a new needle each time you give an APIDRA injection.
- Use BD Ultra-Fine pen needles with the OptiClik. The needles do not come with the APIDRA 3 mL cartridge system or OptiClik. You will need to buy these from a pharmacy. Talk to your healthcare provider if you have questions.
- **Needles, OptiClik and cartridge systems must not be shared.**

### **Getting ready**

Make sure you have the following items:

- OptiClik insulin delivery device
- Pen needles
- Alcohol swab
- APIDRA cartridge system
- Puncture resistant container. See [“How do I dispose of used needles and cartridge systems?”](#)

### **Preparing for an injection**

- Wash your hands with soap and water before you start to touch the cartridge system or the OptiClik.

- Use a new needle for each injection.
- Always perform the safety test before use (see the OptiClik Instruction Leaflet).
- Do not use APIDRA if the solution is colored, cloudy, or if you see particles in it.
- Choose an injection area (for example upper arm, thigh, or stomach area). Change injection sites within the area you choose. **Do not inject into the exact same spot for each injection.**
- After injecting APIDRA, leave the needle in the skin for at least 10 seconds. Then pull the needle straight out. Gently press the injection site for a few seconds. **Do not rub the area.**
- Handle OptiClik<sup>®</sup> with care
- Do not use OptiClik if it is damaged or if you are not sure that it is working correctly.

### **How do I dispose of used needles and cartridge systems?**

- Check with your healthcare provider for instructions about the right way to dispose of used needles and pens. There may be local or state laws about how to dispose of used needles and pens. Do not dispose of used needles or pens in household trash and do not recycle.
- Put used needles and used empty cartridge systems in a container made specially for disposing of used syringes and needles (called a “sharps” container) or a hard plastic container (such as detergent bottles), with a screw-on cap, or metal container with a plastic lid labeled “Used Syringes”. These containers should be sealed and disposed of the right way.

### **How should I store APIDRA cartridge system?**

- Store the opened cartridge system in the OptiClik (Insulin Delivery Device) below 77°F (25°C). Do not refrigerate.
- Keep away from direct heat and light.
- Dispose of any used APIDRA cartridge system 28 days after the first use even if there is insulin left in the cartridge.

If your blood glucose reading is high or low, tell your healthcare provider so the dose can be changed.

If you have lost your OptiClik Instruction Leaflet or have a question, go to [www.opticlik.com](http://www.opticlik.com) or call 1-800-633-1610.

Rev. February 2009

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Bridgewater NJ 08807

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## **PATIENT INSTRUCTIONS FOR USE APIDRA 10 mL vial (100 Units/mL)**

### **This Instructions for Use has two parts:**

#### **Part 1 Use with a syringe**

#### **Part 2 Use with an external insulin infusion pump**

Be sure to read, understand and follow these instructions before taking APIDRA.

### **Part 1 Use with a syringe**

If you will give yourself subcutaneous injections of APIDRA:

- You should take APIDRA within 15 minutes before a meal or within 20 minutes after starting a meal.
- Do not inject APIDRA if you are not going to eat within 15 minutes.
- Inject APIDRA into the skin of your upper arm, thigh, or stomach area. Do not inject APIDRA into a vein or into a muscle.
- Choose an injection area (upper arm, thigh, or stomach area). Change injection sites within the area you choose with each dose. **Do not inject into the exact same spot for each injection.**
- Do not mix APIDRA with insulins other than NPH, for subcutaneous injections. If mixing APIDRA with NPH insulin, draw up APIDRA into the syringe first. Inject the mixture right away.
- Use the needles and syringes prescribed by your healthcare provider.

### **Before every injection make sure you have the following items:**

- Alcohol swabs
- Needle and syringe
- Insulin vial
- Puncture resistant container. See [“How do I dispose of used needles and syringes?”](#).

### **Drawing the insulin into a syringe**

1. Use a new syringe each time you give an injection of APIDRA.

### **Preparing for an injection**

2. Wash your hands with soap and water. Before you start to prepare your injection, check the label to make sure that you are taking the right type of insulin.
3. Look at the APIDRA in the vial. It should look clear. Do not use this vial of APIDRA if the solution is colored, or cloudy, or if you see particles in it.

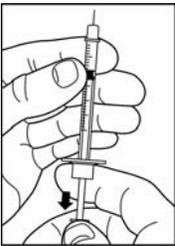
4. If you are using a new vial, remove the protective cap. **Do not** remove the stopper.



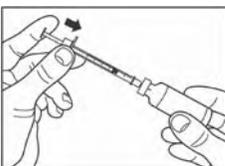
5. Wipe the rubber stopper with an alcohol swab. You do not have to shake the vial of APIDRA before use.



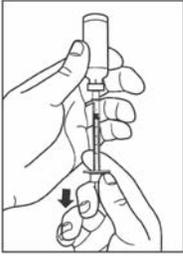
6. Use the needles and syringes prescribed by your healthcare provider. APIDRA 10 mL vials come with 100 units of insulin in 1 mL of APIDRA.
7. Use a new needle and syringe for each injection. Use disposable syringes and needles only one time.
8. Draw air into the syringe equal to the insulin dose prescribed by your healthcare provider.



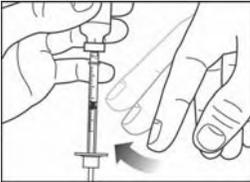
9. Put the needle through the rubber stopper of the vial and push the plunger to inject the air into the vial.



10. Leave the syringe in the vial and turn both upside down. Hold the syringe and vial firmly in one hand.
11. Make sure the tip of the needle is in the insulin solution. With your free hand, pull back on the plunger to draw the correct dose of insulin into the syringe.



- 12 Before you take the needle out of the vial, check the syringe for air bubbles. If you see bubbles in the syringe, hold the syringe straight up and tap the side of the syringe with your finger a few times to make any air bubbles float to the top. Gently push the air bubbles out with the plunger and draw insulin back into the syringe until you have the correct dose. If you are mixing APIDRA with NPH insulin, check with your healthcare provider on how to mix it the right way.



13. Remove the needle from the vial. Do not let the needle touch anything. You are now ready to inject.

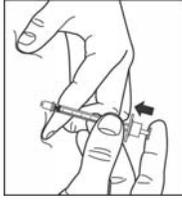
### **Giving the injection**

Do the injection exactly as shown to you by your healthcare provider. Inject APIDRA under your skin.

14. Choose an injection area (for example upper arm, thigh or stomach area). Change injection sites within the area you choose. **Do not inject in the same spot.**  
15. Clean the area with an alcohol swab. Let the injection site dry before you inject.



16. Pinch the skin. Insert the needle into the skin. Release the skin.  
17. Inject the dose by slowly pushing in the plunger of the syringe all the way, making sure you have injected all the insulin. Keep the needle in the skin for at least 10 seconds.



Pull the needle out of your skin, gently press the injection site with a finger for several seconds. **Do not rub the area.**

18. Do not recap the needle. Recapping can lead to a needle stick injury and passing of infection. See “How do I dispose of used needles and syringes?”.  
If your injection is given by another person, this person must also be careful to prevent accidental needle stick injury and passing infections.

### **How do I dispose of used needles and syringes?**

19. Check with your healthcare provider’s office for instructions about the right way to dispose of used needles and syringes. There may be local or state laws about how to dispose of used needles and syringes. Do not dispose of used needles or syringes in household trash and do not recycle them.
20. Put used needles and syringes in a container specially made for throwing away syringes and needles (called a “sharps” container) or a hard plastic container with a screw-on cap or a metal container with a plastic lid labeled “Used Syringes”. These containers should be sealed and dispose of the right way.

See “[How should I store APIDRA?](#)” in the Patient Information leaflet that comes With APIDRA for complete instructions on how to store APIDRA vials.

### **Part 2 Use with an external insulin pump:**

Be sure to read, understand, and follow these instructions before using APIDRA with an external insulin infusion pump. Always read the instruction manual for your pump.

If you will be using an insulin pump:

- APIDRA should be given into the stomach area.
- Change injection sites in the stomach area.
- **Do not mix APIDRA with other insulins and do not dilute APIDRA.**
- Use only insulin pumps that have been specially tested with APIDRA.  
Follow your healthcare provider or pharmacist instructions for which insulin pumps may be used.
- Change the infusion set (reservoir, tubing, and catheter), and the APIDRA in the reservoir every 2 days (48 hours). Change all of these parts sooner if they have been exposed to temperatures higher than 98.6°F (37°C).

### **[Important information about using APIDRA with an external insulin infusion pump](#)**

- **Do not mix APIDRA with any other insulin or liquid when used in a pump.**
- If your APIDRA infusion pump set is not working the right way, you may not get the right amount of insulin that can cause:
  - low blood sugar (hypoglycemia)
  - high blood sugar (hyperglycemia)
  - high amounts of sugar and ketones in your blood or urine
- When you start using APIDRA by infusion pump, your insulin dose may need to be adjusted. Check with your healthcare provider before making any changes to your insulin dose.

### **How to use APIDRA with an external insulin infusion pump?**

- Check with your healthcare provider or pharmacist to see if your pump and infusion set can be used with APIDRA. See the instruction manual of your specific pump on proper use of insulin in a pump. Call your healthcare provider if you have questions about using the pump.
- Change the infusion set, reservoir with insulin, and injection site:
  - at least every 48 hours, change more often than every 48 hours if you have high blood sugar (hyperglycemia), or the pump alarm sounds.
  - if the insulin has been in temperatures over 98.6°F (37°C). Dark colored pump cases or sport covers can increase this type of heat. The location where the pump is worn may affect the temperature.

If you get reactions at the injections infusion site you may need to change infusion sites more often.

### **If your APIDRA infusion pump is not working the right way, follow these steps:**

- Use insulin from a new vial of APIDRA if infusion pump alarms do not respond to all of the following:
  - a repeat injection or bolus of APIDRA
  - a change in the infusion set and the reservoir
  - a change in the infusion injection site
- If the same problems happen again, do not use your infusion pump with APIDRA. You may need to restart insulin injections with syringes and needles.
  - Contact your healthcare provider right away.
  - See section I of the Instructions for Use (“[Use with a syringe](#)”) for the steps for giving injections of APIDRA using syringes and needles.
  - Continue to check your blood sugar often.

**How should I store APIDRA 10 mL vial?**

- Keep in the refrigerator or below 77°F (25°C).
- Keep vials away from direct heat and light.
- Dispose of any opened vial after 28 days after the first use, even if there is insulin left in the vial.

Rev. February 2009

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Bridgewater NJ 08807

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**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

***APPLICATION NUMBER:***  
**NDA 021629/S-008**

**MEDICAL REVIEW(S)**

## **MEDICAL TEAM LEADER MEMO**

Completed February 23, 2009

Hylton V. Joffe, M.D., M.M.Sc.

**NDA:** 21-629; S-008

**Sponsor:** sanofi-aventis

**Drug:** Apidra SoloStar

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This prior approval supplement provides for a new, disposable, 3 mL, prefilled, injector pen (“Apidra SoloStar”) presentation for Apidra, which is a rapid-acting insulin analog approved for the treatment of diabetes mellitus. This is the third review cycle for this supplement. The first cycle ended with an Approvable action on January 18, 2008, because of concerns for confusion between Apidra SoloStar and the already approved Lantus SoloStar product. The second cycle also ended with an Approvable action on July 3, 2008, because the complete response to the first cycle was not deemed adequate to address our deficiencies due to limitations related to the design of the Apidra/Lantus differentiation study. Prior to the Division issuing the second Approvable letter, the sponsor met with FDA and agreed to conduct a new study to show that Apidra SoloStar and Lantus SoloStar are adequately differentiated.

The sponsor obtained feedback on the design for this new study from the Division of Medication Error Prevention and Analysis (DMEPA) prior to study initiation. DMEPA reviewed the study results and concurred with the sponsor that the revised color scheme for the pens (overall error rate 2.7% compared to 20.7% for undifferentiated pens) as well as the revised color scheme for the container and carton labels provide adequate differentiation from Lantus SoloStar. Please see Dr. Judy Park’s review dated December 19, 2008 for further details.

Although not listed as a deficiency in the approvable letters, this supplement also included revisions to the patient labeling documents for the entire Apidra line in accordance with recommendations from the Division of Risk Management (DRISK). Specifically, a single patient package insert (PPI) was developed for all presentations along with Patient Instructions for Use Leaflets for the Apidra vials, Apidra 3 mL cartridge system, and Apidra SoloStar. DRISK provided critical input to ensure that the language for these documents was patient-friendly and that these documents adequately communicated the necessary information pertaining to the use of these products. The sponsor concurred with DRISK’s recommendations. Please see Ms. LaShawn Griffith’s review and Ms. Rachel Hartford’s labeling review for further details.

**Recommendation:** The complete response adequately addresses the deficiencies in the July 2008 Approvable letter. Therefore, this Apidra SoloStar supplement can be approved.

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/s/

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Hylton Joffe  
2/23/2009 09:57:44 PM  
MEDICAL OFFICER

Mary Parks  
2/24/2009 04:53:19 PM  
MEDICAL OFFICER  
concur

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

***APPLICATION NUMBER:***  
**NDA 021629/S-008**

**CHEMISTRY REVIEW(S)**

**NDA 21-629, SCP-008**

**DIVISION OF POST-MARKETING EVALUATION  
Review of Chemistry, Manufacturing, and Controls**

**NDA #: 21-629**

**DATE REVIEWED: 12/12/2007**

**REVIEW #: 2**

**REVIEWER: Donald N. Klein, Ph.D.**

<b><u>SUBMISSION TYPE</u></b>	<b><u>DOCUMENT DATE</u></b>	<b><u>CDER DATE</u></b>	<b><u>ASSIGNED DATE</u></b>
<b><u>N21-081, SCP-024</u></b>			
PA (EDR)	4/21/06	4/24/06	8/15/06
<b><u>N21-629, SCP-008</u></b>			
PA (EDR)	4/21/06	4/24/06	8/15/06
Consult # 1 to CDRH	5/15/06	5/15/06	n/a
CDRH Review # 1	7/10/06	8/15/06 (DFS)	n/a
<b><u>N21-081, SCP-024 &amp; N21-629, SCP-008</u></b>			
<b><u>CMC Review # 1</u></b>	8/16/06	8/17/06	n/a
<b><u>AE Letter for</u></b>			
<b><u>N21-081, SCP-024</u></b>	<b>8/24/06</b>	<b>8/24/06</b>	n/a
<b>(AZ) Response for</b>			
<b>N21-081, SCP-024</b>	10/24/06	10/25/06	10/25/06
Consult # 2 to CDRH	11/12/06	11/15/06	n/a
CDRH Review # 2	2/2/07	9/21/07 (DFS)	n/a
<b><u>N21-081, SCP-024</u></b>			
CMC Review # 2	2/7/07	2/15/07	n/a
<b><u>Approval Letter for</u></b>			
<b>N21-081, SCP-024</b>	4/25/07	4/25/07	n/a
<b><u>(AZ) Response for</u></b>			
<b><u>N21-629, SCP-008</u></b>	<b>9/14/07</b>	<b>9/17/07</b>	<b>10/30/07</b>

**NAME & ADDRESS OF APPLICANT:**

Sanofi-Aventis US  
P.O. Box 6890  
200 Crossing Boulevard  
Bridgewater, NJ 08807-0890

**DRUG PRODUCT NAME:**

Proprietary: Apidra®.  
Established (USAN) (2003): Insulin glulisine.  
Code: HMR 1964  
CAS: 207748-29-6.

**INDICATION:** For treatment of adults with diabetes mellitus for the control of hyperglycemia.

**DOSAGE FORM:** Injectable.

**STRENGTH:** 100U/mL in 3 mL cartridges (OptiClik<sup>®</sup> Pen) and 10 mL vials.

**ROUTE OF ADMINISTRATION:** Subcutaneous.

**Rx/OTC:** Rx

**SPECIAL PRODUCTS:** \_\_ Yes xx No

**SUPPORTING DOCUMENTS:**

1. N21-081, S-011 (OptiClik<sup>®</sup> reusable insulin pen delivery device) was approved on 8/10/04.
2. N21-629, S-002 (OptiClik<sup>®</sup> reusable insulin pen delivery device) was approved on 12/20/05.
3. **Initial Bundle (PA)( 4/24/06):** N21-081, SCP-024 and N21-629, SCP-008 received an AE Letter (8/24/06).
  - a. N21-081, SCP-024: Approved on 4/25/07.

**CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, and MOLECULAR WEIGHT:**

**Chemical Name:** Insulin (human), 3<sup>B</sup>-L-lysine, 29<sup>B</sup>-L-glutamic acid-.

**Molecular formula:** C<sub>258</sub>H<sub>384</sub>N<sub>64</sub>O<sub>78</sub>S<sub>6</sub>.

**MW:** 5822.58.

**CAS:** 207748-29-6.

**Chemical Structure:**



**SUPPLEMENT PROVIDES FOR:** New insulin pen delivery device SoloStar<sup>®</sup>.

**CONSULT:**

1. CDRH (submitted on 5/15/06; completed on 7/10/06; and finalized in DFS on 8/15/06).
2. CDRH (submitted on 2/2/07; completed on 2/23/07; and finalized in DFS on 9/21/07).

**CONCLUSION:** Recommend Approval from the CMC standpoint.

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/s/

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Donald Klein  
12/12/2007 04:59:20 PM  
CHEMIST

Second Review Cycle: DUE 1/17/08; OND Managed; Internal DUE  
date is 12/15/07.

Jim Vidra  
12/13/2007 01:35:32 PM  
CHEMIST

NDA 21-629, SCP-008  
NDA 21-081, SCP-024

**DIVISION OF POST-MARKETING**  
**Review of Chemistry, Manufacturing, and Controls**

NDA #: 21-629  
NDA #: 21-081

DATE REVIEWED: 8/16/2006

REVIEW #: 1

REVIEWER: Donald N. Klein, Ph.D.

<u>SUBMISSION TYPE</u>	<u>DOCUMENT DATE</u>	<u>CDER DATE</u>	<u>ASSIGNED DATE</u>
N21-081 PA (EDR)	4/21/06	4/24/06	8/15/06
N21-620 PA (EDR)	4/21/06	4/24/06	8/15/06
Consult to CDRH	5/15/06	5/15/06	n/a
CDRH review	7/10/06	8/15/06 (DFS)	n/a

NAME & ADDRESS OF APPLICANT:

Sanofi-Aventis U.S. LLC  
300 Somerset Corporate Blvd.  
Bridgewater, NJ 08807

DRUG PRODUCT NAME:

N21-629 Proprietary: Apidra®  
Nonproprietary (USAN)(2003): Insulin glulisine.  
CAS: 207748-29-6.  
Code: HMR 1964.

N21-081 Proprietary: Lantus®  
Nonproprietary (USAN)(1999): Insulin glargine.  
CAS: 160337-95-1.  
Code: HOE 901 and HOE 71GT.

INDICATION: **N21-629:** For the treatment of adults with diabetes mellitus for the control of hyperglycemia.

**N21-081:** For the treatment of adults and pediatric patients with Type 1 diabetes mellitus or adult patients with Type 2 diabetes mellitus who require basal (long acting) insulin for the control of hyperglycemia.

DOSAGE FORM: **N21-629 and N21-081:** Injectable.

STRENGTHS: **N21-629 and N21-081:** 100 IU/mL in 3 mL cartridges (OptiClik® Pen) and 10 mL vials.

**ROUTE OF ADMINISTRATION:** N21-629 and N21-081: Injection.

**Rx/OTC:** Rx.

**SPECIAL PRODUCTS:** \_\_ Yes **xx** No

**CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, and MOLECULAR WEIGHT:**

**N21-629:** (1) Insulin (human), 3<sup>B</sup>-L-lysine, 29<sup>B</sup>-L-glutamic acid-;  
(2) [3<sup>B</sup>-L-Lysine, 29<sup>B</sup>-L-glutamic acid]insulin (human).



MW: 5822.58 daltons.



**N21-081:** (1) Insulin (human), 21<sup>A</sup>-glycine-30<sup>B</sup>a-L-arginine-30<sup>B</sup>b-L-arginine-;  
(2) 21<sup>A</sup>-Glycine-30<sup>B</sup>a-L-arginine-30<sup>B</sup>b-L-arginine insulin (human).



MW: 6062.89 daltons.



**SUPPLEMENT PROVIDES FOR:** New insulin pen delivery device SoloStar<sup>®</sup>.

**SUPPORTING DOCUMENTS:** N21-081, S-011 (OptiClik<sup>®</sup> reusable insulin pen delivery device) was approved on 8/10/04; N21-629, S-002 (OptiClik<sup>®</sup> reusable insulin pen delivery device) was approved on 12/20/05.

**CONSULT:** CDRH (submitted 5/15/06; completed 7/10/06; in DFS on 8/15/06).

N21-629, SCP-008  
N21-081, SCP-024

*Apidra Injection, Aventis*  
*Lantus Injection, Aventis*

3

**CONCLUSIONS: From the CMC standpoint approvable is recommended.**

(b) (4)

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Donald Klein  
8/16/2006 06:05:31 PM  
CHEMIST

These PAs were assigned to me yesterday.

Jim Vidra  
8/17/2006 08:35:42 AM  
CHEMIST

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

***APPLICATION NUMBER:***  
**NDA 021629/S-008**

**OTHER REVIEW(S)**

**Division of Metabolism and Endocrinology Products**

**REGULATORY PROJECT MANAGER REVIEW**

**Application Number:** NDA 21-629/S008

**Name of Drug:** Apidra (insulin glulisine [rDNA origin] injection)

**Applicant:** sanofi-aventis

**Material Reviewed:**

<b>Submission &amp; Receipt Date</b>	<b>Document Type</b>
January 30, 2009	Proposed Apidra Package Insert (PI), Patient Package Insert (PPI), Instructions for Use Leaflets (Vial, Cartridge, and SoloStar)
September 15, 2008	Apidra SoloStar Carton and Container Labels

**Material Referenced:**

<b>Date Finalized</b>	<b>Author (Discipline)</b>	<b>Document Type</b>
January 14, 2009	LaShawn Griffiths Division of Risk Management (DRISK) Office of Surveillance and Epidemiology (OSE)	Review of Apidra PI and PPI, Apidra SoloStar Instructions for Use Leaflet (IFUL), and Apidra Cartridge IFUL and Vial IFUL
December 19, 2008	Judy Park Division of Medication Error and Prevention and Analysis (DMEPA) OSE	Review of Apidra SoloStar Carton label, container label
October 24, 2008	Rachel Hartford Regulatory Project Manager Division of Metabolism and Endocrinology Products (DMEP)	NDA 21-629 Supplement 015 Approval Letter
July 3, 2008	Rachel Hartford Regulatory Project Manager DMEP	NDA 21-629 Supplement 008 Approvable Letter
June 10, 2008	Judy Park Division of Medication Error Prevention OSE	Review of March 3, 2008 Apidra SoloStar carton label, container label, and IFUL

May 23, 2008	Melina Griffis Division of Medication Errors and Technical Support (DMETS) OSE	Evaluation of the factors contributing to confusion between Apidra and Lantus
March 20, 2008	Sharon Mills Division of Risk Management (DRISK) OSE	Supplement 015 Review of Patient Labeling (combined PPI/IFULs) for Vial and Cartridge Packaging Configurations submitted June 27, 2007
January 17, 2008	Rachel Hartford Regulatory Project Manager DMEP	NDA 21-629 Supplement 008 Approvable Letter
January 4, 2007	Sharon Mills DRISK OSE	Review of Patient Labeling submitted September 14, 2007; Apidra SoloStar combined PPI/IFUL
January 4, 2007	Judy Park DMETS OSE	Review of the proposed name, product design, carton label, container label, Apidra SoloStar combined PPI/IFUL, (b) (4)
August 24, 2006	Enid Galliers Chief, Project Management Staff DMEP	NDA 21-629 Supplement 008 Approvable Letter

### **Background and Summary**

NDA 21-629 for Apidra (insulin glulisine [rDNA origin]) Injection, an analog of human insulin, was approved on April 16, 2004, for the treatment of adult patients with diabetes mellitus, for the control of hyperglycemia.

This supplement providing for the addition of the Apidra SoloStar Disposable injector pen was submitted on April 24, 2006. Approvable letters were issued on August 24, 2006, January 18, 2008, and July 3, 2008. On September 15, 2008, sanofi-aventis submitted a complete response to the July 3, 2008, approvable letter.

Supplement 015 was approved on October 24, 2008; it provided for use of Apidra in patients 4 through 17 and triggered PLR conversion. The DRISK review for Supplement 015 recommended converting the combined cartridge PPI/IFUL and combined vial PPI/IFUL into one PPI for all Apidra products and separate Patient Instruction for Use Leaflets for each Apidra presentation (cartridge and vial). Implementation was combined with Supplement 008.

Approval of this supplement will result in the following new labeling pieces: Apidra PPI, Apidra SoloStar Carton, Apidra SoloStar Container, Apidra SoloStar IFUL, Apidra Cartridge IFUL, and Apidra Vial IFUL.

## Review

1. The Package Insert submitted on January 30, 2009, was compared to the currently approved Package Insert, approved on October 24, 2008. The following changes have been made:
  - a. 3 mL SoloStar prefilled pen was added to the DOSAGE FORMS AND STRENGTHS sections
  - b. The revision date was changed to February 2009 from October 2008
  - c. Italicized [See Drug Interactions (7)] in the second paragraph of section 5.2 Hypoglycemia
  - d. Changed U to Units in section 8.1 Pregnancy
  - e. Italicized [See Warnings and Precautions (5.1)] in the Hepatic Impairment portion of section 12.4 Clinical pharmacology in specific populations
  - f. Changed the 6<sup>th</sup> line in table 9 to “Adjusted mean change from baseline” from “Adjusted mean change from Baseline”
  - g. Added “3 mL SoloStar prefilled pen, package of 5 NDC 0088-2502-05” to 16.1 How supplied
  - h. Added the following to section 16 HOW SUPPLIED/STORAGE AND HANDLING
    - 1) Pen needles are not included in the packs.
    - 2) BD Ultra-Fine™ pen needles<sup>†</sup> to be used in conjunction with OptiClik are sold separately and are manufactured by Becton Dickinson and Company.
    - 3) SoloStar is compatible with all pen needles from Becton Dickinson and Company, Ypsomed and Owen Mumford.
  - i. In section 16.2 Storage
    - 1) added “(see carton and container)” to “Do not use after the expiration date
    - 2) added “/SoloStar” to “Unopened Vial/Cartridge System”
    - 3) added the following subsection: Open (In-Use) SoloStar prefilled pen: The opened (in-use) SoloStar should NOT be refrigerated but should be kept below 77°F (25°C) away from direct heat and light. The opened (in-use) SoloStar kept at room temperature must be discarded after 28 days.
  - j. Changed the “Handling” to “handling” in section 16.3 Preparation and handling

- k. Updated the copyright date to 2009 from 2008
- 2. Approval of this supplement will result in the following new labeling pieces: Apidra PPI, Apidra SoloStar Carton, Apidra SoloStar Container, Apidra SoloStar IFUL, Apidra Cartridge IFUL, and Apidra Vial IFUL. The currently approved (October 24, 2008) combined Apidra Cartridge PPI/IFUL and combined Apidra Vial PPI/IFUL will cease to exist upon approval of this supplement.

3. Highlights of the new Apidra PPI:

- a. Simplified wording and clarified concepts to lower the readability scores
- b. Added lay definitions of technical terms
- c. The following statement was added: “Call your doctor for medical advice about side effects. You may report side effect to FDA at 1-800-FDA-1088.”
- d. The information in the section “Who should not take Apidra?” was changed to reflect the labeled contraindications

e. [Redacted] (b) (4)

f. Added a sentence stating [Redacted] (b) (4)

g. [Redacted] (b) (4)

h. Use the term “healthcare provider” instead of [Redacted] (b) (4)

i. [Redacted] (b) (4)

j. [Redacted] (b) (4)

4. Highlights of the new Apidra Cartridge and Apidra Vial IFULs

a. [Redacted] (b) (4)

b. Simplified wording and clarified concepts to lower the readability scores

c. Added lay definitions of technical terms

- d. Labeled figures and referenced the figures in the text for the Apidra Vial IFUL
- e. Use the term “healthcare provider” instead of (b) (4)

### **Conclusion**

The numerous labeling modifications were cleared through: DMEP, DMEPA, and DRISK. The final Apidra SoloStar carton and container labels were submitted on September 15, 2008. The final versions of the Apidra PI, Apidra PPI, Apidra SoloStar IFUL, Apidra Cartridge IFUL, and Apidra Vial IFUL were submitted on January 30, 2009. All final labeling pieces were agreed upon by the FDA and sanofi-aventis. An approval letter should be drafted for S-008.

Reviewed by:  
Rachel Hartford  
Regulatory Project Manager

Supervisory concurrence:  
Enid Galliers  
Chief, Project Management Staff

Drafted: 5Feb2008  
Revised: 12, 19, and 23Feb09  
Finalized: 23Feb09

CSO LABELING REVIEW

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

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Rachel E Hartford  
2/24/2009 09:03:11 AM  
CSO



**Department of Health and Human Services  
Public Health Service  
Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Surveillance and Epidemiology**

Date: January 14, 2009

To: Mary Parks, M.D., Director  
**Division of Metabolism and Endocrinology Products (DMEP)**

Through: Jodi Duckhorn, M.A., Team Leader  
**Patient Labeling and Education Team  
Division of Risk Management (DRISK)**

From: LaShawn Griffiths, MSHS-PH, BSN, RN  
Sharon Mills, BSN, RN, CCRP  
Patient Product Information Reviewers  
**Patient Labeling and Education Team  
Division of Risk Management (DRISK)**

Subject: Review of Patient Labeling (PPI and Patient Instructions for Use)

Drug Name(s) and Application Numbers: Apidra (insulin glulisine [rDNA origin] injection)  
NDA 21-629/S-008

Applicant/sponsor: Sanofi Aventis

OSE RCM #: 2008-201

## **1 INTRODUCTION**

Sanofi Aventis submitted a Complete Response to New Drug Application (NDA) 21-629 on March 3, 2008 in response to the Agency's Approvable letter dated January 18, 2008. The submission included revised Patient Instructions for Use for Apidra SoloStar.

Apidra currently has two approved product presentations, 10 mL vial and 3 mL cartridge system (300 units per cartridge system) 100 units per mL (U-100) for use with the OptiClik insulin pen.

DMEP requested that DRISK'S Patient Labeling and Education Team review the revised Patient Labeling in the form of a PPI, and Patient Instructions for Use for the Apidra SoloStar 3 mL cartridge system, Apidra 10 mL vials, and Apidra SoloStar prefilled pen. This review is written in response to that request.

OSE previously reviewed the Patient Labeling for Apidra on the following dates: January 15, 2003, April 8, 2004, May 31, 2007, January 4, 2008, and March 20, 2008. We note that DMEP conveyed to the sponsor that it would be acceptable to bundle the PPI for the S-015 based on OSE's PPI review dated March 20, 2008, with the revisions to the PPI for S-008. S-015 was approved without changes to the PPI.

## **2 MATERIAL REVIEWED**

- Revised DRAFT Apidra Professional Information (PI) submitted by Sanofi Aventis on November 10, 2008.
- Revised DRAFT Apidra Patient Package Insert (PPI) submitted by Sanofi Aventis on August 19, 2008.
- Revised DRAFT Apidra vial Patient Instructions for Use (IFU) submitted by Sanofi Aventis on August 19, 2008.
- Revised DRAFT Apidra cartridge Patient Instructions for use (IFU) submitted by Sanofi Aventis on August 19, 2008.
- Revised DRAFT Apidra SoloStar prefilled pen Instruction Leaflet (IFU) submitted by Sanofi Aventis on March 3, 2008.

## **3 DISCUSSION**

The purpose of patient directed labeling is to facilitate and enhance appropriate use and provide important risk information about medications. Our recommended changes are consistent with current research to improve risk communication to a broad audience, including those with lower literacy.

To enhance patient comprehension, materials should be written at a 6<sup>th</sup> to 8<sup>th</sup> grade reading level, and have a reading ease score of at least 60% (60% corresponds to an 8<sup>th</sup> grade reading level). The reading scores for each of the documents as submitted by the sponsor and also with our recommended changes are indicated in section 4 below.

In our review of the PPI and IFUs, we have:

- simplified wording and clarified concepts where possible,
- ensured consistency with the PI,
- removed unnecessary or redundant information,
- ensured that the PPI meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006).

In 2008, The American Society of Consultant Pharmacists Foundation in collaboration with The American Foundation for the Blind published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. They recommend using fonts such as Arial, Verdana, or APFont to make medical information more accessible for patients with low vision. We recommend that the Sponsor reformat the PPI and IFUs using the font APFont, which was developed by the American Printing House for the Blind specifically for low vision readers.

All future relevant changes to the PI should also be reflected in the PPI and IFUs as appropriate.

#### 4 CONCLUSIONS AND RECOMMENDATIONS

##### **Apidra Patient Package Insert (PPI) for 3 mL cartridge, 10 mL vial, and SoloStar Prefilled Pen**

1. The sponsor's proposed PPI has the following readability scores:

- Flesch Reading Ease: 50.6%
- Flesch-Kincaid Grade Level: 9.4

The sponsor's readability scores for the PPI are higher than that recommended for optimal patient comprehension. We recommend that the sponsor simplify the PPI by incorporating our recommendations.

Our revised PPI has the following readability scores:

- Flesch Reading Ease: 54.0%
- Flesch-Kincaid Grade Level: 8.8

2.  (b) (4)

While we realize this recommendation is not consistent with our previous review of APIDRA (dated January 15, 2003), this recommendation is consistent with current thinking that the  (b) (4) section be reserved for the most serious information a patient needs to know. Typically, this section is reserved for products with Medication Guides. The information in this section is still included in the PPI, but moved to a different section.

3. We deleted the section  (b) (4). If retained, the disease specific information can be placed at the end of the PPI. We prefer that information about the disease be addressed separate from the product specific information.

 (b) (4)

4. [REDACTED] (b) (4)
5. In the section, “What are the possible side effects of APIDRA?” the sponsor list (b) (4) as a symptom of “low blood sugar” fast heartbeat is tachycardia; [REDACTED] (b) (4). The sponsor should clarify the adverse event in the PI and make it consistent in the PPI. The proposed section about [REDACTED] (b) (4) was deleted as this is not an adverse reaction to Apidra. [REDACTED] (b) (4)
6. Section 16.2 of the PI states “Do not use after expiration date”. However, neither the PI nor the proposed PPI state where the expiration date is found. The sponsor should add this information to the PI and then it can be added to the PPI. The language in the PPI must be consistent with the language in the PI.

#### **Apidra 10 mL vial Patient’s Instructions for Use (IFU)**

1. The sponsor’s proposed Patient Instructions for Use has the following readability scores:
  - Flesch Reading Ease: 66.2%
  - Flesch-Kincaid Grade Level: 7.1

The readability scores of the vial IFU as proposed by the sponsor are acceptable.

Our revised IFU has the following readability scores:

- Flesch Reading Ease: 62.1%
  - Flesch-Kincaid Grade Level: 7.8
2. The sponsor’s proposed vial Patient Instructions for Use includes use with syringe as well as with an external pump.
  3. The sponsor should label each figure and reference each figure in the text as appropriate. Sponsor should also enlarge the figures so the details can be seen more clearly.
  4. The sponsor should add a list of items needed to give an injection of APIDRA with a syringe and needle, including a “sharps” container.

#### **Apidra 3 mL cartridge system for use in OptiClik Insulin Delivery Device (IFU)**

1. The sponsor’s proposed Patient Instructions for Use have the following readability scores:
  - Flesch Reading Ease: 57.6%
  - Flesch-Kincaid Grade Level: 8.5

We recommend that the sponsor simplify the IFU by incorporating our recommended changes.

Our revised IFU has the following readability scores:

- Flesch Reading Ease: 61.8%
- Flesch-Kincaid Grade Level: 8.5

2. [REDACTED] (b) (4)
3. [REDACTED] (b) (4)
4. The Review Division should verify that the sponsor should not refer to the OptiClik as a [REDACTED] and use language about [REDACTED] in this IFU since it pertains to needles, cartridges, and the OptiClik which is listed as an Insulin Delivery Device in section 16.1 “How supplied” in the PI.
5. The sponsor should list all items needed to give an injection using the Apidra 3 mL cartridge system, including a “sharps” container. Add a figure identifying all necessary items.
6. [REDACTED] (b) (4)

#### **Apidra SoloStar Prefilled Pen Patient’s Instructions for Use (IFU)**

1. The sponsor’s proposed Patient Instructions for Use have the following readability scores:
  - Flesch Reading Ease: 52.4%
  - Flesch-Kincaid Grade Level: 10.6

The sponsor’s readability scores for the IFU are higher than that recommended for optimal patient comprehension. We recommend that the sponsor simplify the IFU by incorporating our recommended changes.

Our revised IFU has the following readability scores:

- Flesch Reading Ease: 69.0%
- Flesch-Kincaid Grade Level: 7.8

2. The sponsor should add figures to go with each step. Each figure should be labeled, and referenced in the text as appropriate.
3. The sponsor should label the plunger in the figure showing the pen parts.
4. The sponsor should clarify whether the needles are specifically pen needles. If so, clarify in PI section 16.1 “How supplied” and in the Patient Instructions for Use. The figure has a label for a pen needle, but it is not stated in the PI or elsewhere in the Patient Instructions for use.

Please contact us with any concerns or questions.

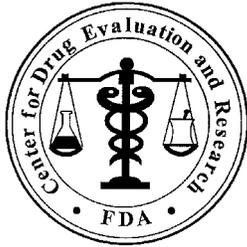
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/s/

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LaShawn Griffiths  
1/14/2009 11:49:45 AM  
DRUG SAFETY OFFICE REVIEWER

Jodi Duckhorn  
1/14/2009 01:39:13 PM  
DRUG SAFETY OFFICE REVIEWER



**Department of Health and Human Services  
Public Health Service  
Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Surveillance and Epidemiology**

Date: December 18, 2008

To: Mary Parks, MD, Director  
Division of Metabolic and Endocrinology Products

Thru: Kellie Taylor, PharmD, MPH, Team Leader  
Carol Holquist, RPh, Director  
Division of Medication Error Prevention and Analysis

From: Judy Park, PharmD, Safety Evaluator  
Division of Medication Error Prevention and Analysis

Subject: Labeling Review

Drug Name: Apidra SoloStar (Insulin Glulisine [rDNA origin] Injection)

Submission Number: S-008

Application Type/Number: NDA 21-629

Applicant/Applicant: sanofi-aventis

OSE RCM #: 2008-1518

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## EXECUTIVE SUMMARY

The Label and Labeling Risk Assessment findings and the data provided from the differentiation study indicate that the presentation of information and design of the proposed container labels and carton labeling adequately minimize the potential for medication errors with Lantus SoloStar and Apidra SoloStar. The Division of Medication Error Prevention and Analysis believes the Applicant adequately addressed the deficiencies cited in the Approvable Letter dated July 3, 2008 and the data submitted shows that the two pens, Lantus SoloStar and Apidra SoloStar, are adequately distinguishable. Thus, DMEPA finds the proposed labels and labeling acceptable for approveable.

### 1 BACKGROUND

#### 1.1 INTRODUCTION

This consult was written in response to a request from the Division of Metabolic and Endocrinology Products (DMEP) to review the complete response submitted by the Applicant on September 15, 2008 along with the revised container label, carton labeling, and differentiation study between Lantus SoloStar and Apidra SoloStar. The Division of Risk Management was also internally consulted to review the differentiation study.

#### 1.2 REGULATORY HISTORY

The Applicant submitted a Supplemental NDA on April 21, 2006 for the addition of Apidra SoloStar (NDA 21-629/S-008) and Lantus SoloStar (NDA 21-081/S-024), disposable insulin injector pens to their insulin product lines. Both supplements received an “approveable” letter on August 24, 2006 citing stability, device, and labeling deficiencies. Subsequently, Lantus SoloStar received an approval action on April 25, 2007.

Following the approval of Lantus SoloStar, the following actions have occurred with the Apidra SoloStar application:

- On September 14, 2007, the Applicant submitted a complete response to the remainder of the questions relating to Apidra SoloStar that were posed in the August 24, 2006 approveable letter.
- On January 18, 2008, a second approveable letter was issued based on concerns revised in OSE Review #06-0106 and #06-0179, dated August 24, 2006. At that time, we had no objection to the use of the proprietary name. We reviewed the labels and labeling in OSE Review #2007-2373 dated January 4, 2008 which found the proposed container labels and carton labeling were vulnerable to confusion with Lantus SoloStar.
- On March 3, 2008, the Applicant submitted complete response to the approveable letter issued on January 18, 2008.
- On June 11, 2008, a meeting between the Applicant and the Agency was held and it was agreed that an (b) (4) differentiation study with an (b) (4) study design will be conducted to show that Lantus SoloStar and Apidra SoloStar are adequately differentiated (b) (4)
- On July 3, 2008, another approveable letter was issued because the revised labels and labeling and the differentiation study did not adequately address the concerns with confusion between Lantus SoloStar and Apidra SoloStar (OSE Review #2008-465 dated June 3, 2008).

- On July 27, 2008, a supplement request letter from the Agency was sent to the Applicant with suggestions for an alternate study design.
- On September 15, 2008, the Applicant submitted a complete response to the approvable letter with revised container label, carton labeling, and a new differentiation study between Lantus SoloStar and Apidra SoloStar for review and comment.

### **1.3 PRODUCT INFORMATION**

Apidra (insulin glulisine [rDNA origin] injection) is a human insulin analog that is a rapid-acting, parenteral blood glucose lowering agent. Apidra is indicated for the treatment of adult patients with diabetes mellitus for the control of hyperglycemia. Apidra has a more rapid onset of action and a shorter duration of action than regular human insulin. Apidra should normally be used in regimens that include a longer-acting insulin or basal insulin analog. Apidra should be given within 15 minutes before a meal or within 20 minutes after starting a meal. Apidra is intended for subcutaneous administration and for use by external infusion pump. The dosage of Apidra should be individualized and determined based on the physician's advice in accordance with the needs of the patient. Apidra SoloStar will be available as a 3 mL prefilled pen.

## **2 METHODS AND MATERIALS**

This section describes the methods and materials used by the Division of Medication Error Prevention and Analysis (DMEPA) staff to conduct a label, labeling, and/or packaging risk assessment. Additionally, results from a differentiation study between Lantus SoloStar and Apidra SoloStar was submitted by the Applicant.

The primary focus of the assessments is to identify and remedy potential sources of medication error prior to drug approval. We define a medication error as any preventable event that may cause or lead to inappropriate medication use or patient harm while the medication is in the control of the health care professional, patient, or consumer.<sup>1</sup>

### **2.1 LABEL AND LABELING**

In addition to reviewing the study finding, DMEPA conducted an evaluation of the container labels and carton labeling for Apidra SoloStar. The label and labeling of a drug product are the primary means by which practitioners and patients (depending on configuration) interact with the pharmaceutical product. The container labels and carton labeling communicate critical information including proprietary and established name, strength, form, container quantity, expiration, and so on.

Given the critical role that the label and labeling has in the safe use of drug products, it is not surprising that 33 percent of medication errors reported to the USP-ISMP Medication Error Reporting Program may be attributed to the packaging and labeling of drug products, including 30 percent of fatal errors.<sup>2</sup>

Because our staff analyze reported misuse of drugs, our staff are able to use this experience to identify potential errors with all medication similarly packaged, labeled or prescribed. We use Failure Mode and Effects Analysis (FMEA) and the principles of human factors to identify

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<sup>1</sup> National Coordinating Council for Medication Error Reporting and Prevention. <http://www.nccmerp.org/aboutMedErrors.html>. Last accessed 10/11/2007.

<sup>2</sup> Institute of Medicine. Preventing Medication Errors. The National Academies Press: Washington DC. 2006. p275.

potential sources of error with the proposed product labels and insert labeling, and provided recommendations that aim at reducing the risk of medication errors.

For this complete response, the Applicant submitted on September 15, 2008 the following pens, labels and labeling for evaluation (see Appendices A and B for images):

- Apidra SoloStar Container
- Apidra SoloStar Carton

We also reviewed the deficiencies outlined in the July 3, 2008 approvable letter and the items described in the supplement request letter dated June 27, 2008 with suggestions for the alternate study design.

## **2.2 DIFFERENTIATION STUDY BETWEEN LANTUS SOLOSTAR AND APIDRA SOLOSTAR**

DMEPA reviewed and evaluated the data collected from a differentiation study between Lantus SoloStar and Apidra SoloStar conducted by an independent consulting firm dated September 10, 2008. This study was conducted at the request of DMEPA because of the medication error reports of confusion between the currently marketed Lantus and Apidra products.

The study utilized color differentiated pens (see Appendix C) which represent the proposed pens for approval and undifferentiated pens (see Appendix D) which are identical in every respect except for the proprietary and established names on the labels. The design of the study was intended to assess if diabetes patients can correctly identify which pen to use in different scenarios calling for once-a-day (Lantus SoloStar) or three-times-a-day (Apidra SoloStar) insulin. The primary outcome was the error percentage rate which was calculated as the total observed number of incorrect selection or inability to select the correct pen in the three scenarios over the total number of observations (three scenarios per subject). In each scenario, the respondents were also asked for reasons for choosing the specific pen.

In addition, there was a fourth scenario in the study designed to assess the influence of confirmation bias when identifying the SoloStar pens in isolation of one another. In this scenario, patients were presented with Apidra SoloStar or Lantus SoloStar in isolation and asked to indicate if it was the correct pen to use in two scenarios of usage directions.

## **3 RESULTS**

### **3.1 LABELS AND LABELING**

The Applicant has provided adequate data from the study to support that the proposed name and color scheme for the pen, container and carton labels for Apidra SoloStar provide differentiation from the Lantus SoloStar product. The study design was in accordance with the Agency's suggestions. We did not identify any outstanding or new areas of concern with respect to the proposed Apidra SoloStar labels.

### **3.2 DIFFERENTIATION STUDY BETWEEN LANTUS SOLOSTAR AND APIDRA SOLOSTAR**

The study involved 200 diabetic patients who were randomized to either differentiated (100 patients) or undifferentiated (100 patients) pens. The differentiation exercise involving three scenarios showed 98%, 96% and 98% correct response for the differentiated pens versus 79%, 79% and 80% for the undifferentiated pens. The combined error rate of the three scenarios was statistically different between the pens (2.7% for the differentiated pens versus 20.7% for the undifferentiated pens) as shown on Table 2 on page 7.

**Table 2: Error Percentage Rate between Lantus SoloStar and Apidra SoloStar**

<b>Scenario</b>	<b>Color differentiated SoloStar Pens Error Percentage Rate</b>	<b>Undifferentiated SoloStar Pens Error Percentage Rate</b>
1	2%	21%
2	4%	21%
3	2%	20%
<i>Overall</i>	<i>2.7%</i>	<i>20.7%</i>

The top reasons of why patients chose the incorrect pen or had unsure responses in the arm with the differentiated pens included the incorrect association of pen with usage direction or just guessed. The reasons in the arm with the undifferentiated pens were because they associated the incorrect usage direction with the wrong pen, “look the same,” “don’t know which is which,” or “can’t tell them apart.” After the three scenarios, the patients were asked if they would have trouble remembering that the pens are different and 90% in the differentiated arm responded they would not have trouble remembering as opposed to 49% in the undifferentiated arm.

When Apidra SoloStar was presented in isolation to identify the correct response in two different scenarios, the incorrect responses were 4% and 0% in the differentiated arm and 25% and 23% in the undifferentiated arm. Correct responses were 96% and 100% in the differentiated arm versus 75% and 77% in the undifferentiated arm.

#### **4 DISCUSSION**

Upon review of the revised proposed label and labeling, DMEPA finds them acceptable. The results from the differentiation study support that the visual differences (color, container label, format and design) between the two pens, Lantus SoloStar and Apidra SoloStar, provide assurance that the differentiation is adequate so that patients can distinguish between the pair and in isolation from one another.

(b) (4), this study provided a baseline error rate by studying the undifferentiated pens as control and comparing the baseline error rate to the differentiated pens which are the proposed pens for approval. However, there were some limitations of the study such as, not all patients received the same pen (some received differentiated pens, some received undifferentiated pens) therefore each subject was not their own control. Another limitation was that the study was conducted in an artificial setting (i.e. not in the home environment where patients are likely to use the products), and specifically being asked to observe the pens which may not translate into real practice setting. Therefore, although we find the Applicant’s efforts to provide visual distinction acceptable, we expect, and the study results support, that some potential for confusion still exists.

The Division of Risk Management (DRISK) also reviewed the results of the differentiation study with the following assessment:

*DRISK has reviewed the Lantus SoloStar and Apidra SoloStar differentiation study conducted by Sanofi-Aventis. After reviewing the results of the study, DRISK agrees with the conclusions drawn by the sponsor that diabetes patients can adequately distinguish between the Lantus SoloStar and Apidra SoloStar pens based on the difference in color and label. DRISK reviewed the DMEPA labeling review memo for Apidra SoloStar and agrees with the summary of the color differentiation study that the pens are adequately*

*different and patients can distinguish between the two. DRISK has no additional comments about the differentiation study.*

Based upon overall assessment of the complete response, labels, labeling, and differentiation study, we believe the Applicant has adequately addressed the deficiencies cited in the Approvable Letter dated July 3, 2008.

## **5 CONCLUSIONS AND RECOMMENDATIONS**

Based upon our assessment of the complete response, labels, labeling, and differentiation study, the Division of Medication Error Prevention and Analysis believes the Applicant has adequately addressed the deficiencies cited in the Approvable Letter dated July 3, 2008 and finds the proposed labels and labeling acceptable for approvable.

We would appreciate feedback on the final outcome of this review. Please copy us on any communication to the Applicant with regard to this review. We would be willing to meet with the Division for further discussion, if needed. If you have further questions or need clarifications, please contact Cheryl Campbell, Project Manager, at 301-796-0723.

### **5.1 COMMENTS TO THE APPLICANT**

Based upon our assessment of the complete response, labels, labeling, and differentiation study, the Division of Medication Error Prevention and Analysis believes the Applicant has adequately addressed the deficiencies cited in the Approvable Letter dated July 3, 2008 and finds the proposed labels and labeling acceptable for approvable.

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/s/

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Judy Park  
12/18/2008 04:41:15 PM  
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Kellie Taylor  
12/18/2008 05:36:56 PM  
DRUG SAFETY OFFICE REVIEWER

Carol Holquist  
12/19/2008 08:29:03 AM  
DRUG SAFETY OFFICE REVIEWER



**Department of Health and Human Services  
Public Health Service  
Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Surveillance and Epidemiology**

Date: June 4, 2008

To: Mary Parks, MD, Director  
Division of Metabolic and Endocrinology Products

Thru: Kellie Taylor, PharmD, MPH, Team Leader  
Carol Holquist, RPh, Director  
Division of Medication Error Prevention

From: Judy Park, PharmD, Safety Evaluator  
Division of Medication Error Prevention

Subject: Labeling Review

Drug Name: Apidra SoloStar (Insulin Glulisine [rDNA origin] Injection)

Submission Number: S-008

Application Type/Number: NDA 21-629

Applicant/Applicant: Sanofi-Aventis

OSE RCM #: 2008-465

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## **EXECUTIVE SUMMARY**

Following the evaluation of the complete response submitted by the Applicant along with the revised container labels, carton labeling, and Information Leaflet submitted on March 3, 2008, we have identified several areas that contribute to medication errors.

The Label and Labeling Risk Assessment findings indicate that the presentation of information and design of the proposed container labels and carton labeling introduces vulnerability to confusion that could lead to medication errors. We do not believe the Applicant adequately addressed the deficiencies cited in the Approvable Letter dated January 18, 2008 (b) (4)

Although we acknowledge that the revised labels appear to be better differentiated from Lantus SoloStar labels in isolation than the previously submitted labels, (b) (4)

The Applicant has not provided the Agency with data from studies to support that the revised color scheme provides adequate differentiation from Lantus SoloStar despite the fact that this was recommended in the approval letter dated January 17, 2008. We were provided with data in the complete response dated September 14, 2007 that indicated a significant percentage of color-blinded respondents could not perceive the pens as different or perceive the correct colors. Thus, it remains unclear to us if the proposed labels and labeling changes adequately address the concerns we outlined in the approvable letter. However, we find the revised Instruction Leaflet to address the plunger issue acceptably.

The Division of Medication Error Prevention believes the risks we have identified can be addressed and mitigated prior to drug approval, and provides recommendations in Section 5.2 that aim at reducing the risk of medication errors.

## **1 BACKGROUND**

### **1.1 INTRODUCTION**

This consult was written in response to a request from the Division of Metabolic and Endocrinology Products to review the complete response submitted by the Applicant on March 3, 2008 along with the revised container label, carton labeling, and Instruction Leaflet.

### **1.2 REGULATORY HISTORY**

The Applicant submitted a Supplemental NDA on April 21, 2006 for the addition of Apidra SoloStar (NDA 21-629/S-008) and Lantus SoloStar (NDA 21-081/S-024), disposable insulin injector pens to their product line. Both supplements received an “approvable” letter on August 24, 2006 citing stability, device, and labeling deficiencies. Subsequently, Lantus SoloStar received an “approval” action on April 25, 2007. On September 14, 2007, the Applicant submitted a complete response to the remainder of the questions relating to Apidra SoloStar that were posed in the August 24, 2006 approvable letter.

The Division of Medication Error Prevention previously reviewed the proposed name, Apidra SoloStar, in the OSE Review #06-0106 and #06-0179, dated August 24, 2006. At that time, we had no objections to the use of the proprietary name. We reviewed the labels and labeling in OSE

Review #2007-2373 dated January 4, 2008 and found the proposed container labels and carton labeling were vulnerable to confusion with Lantus SoloStar. We concluded, and DMEP concurred, that the September 14, 2007 submission did not adequately address the concerns expressed on the April 24, 2007 approvable letter. Thus, the supplement received another “approvable” letter on January 18, 2008.

The Approvable Letter sent to the Applicant on January 18, 2008 cited two deficiencies: (b) (4)

(b) (4) and conducting (b) (4) studies to provide the Agency with reasonable assurance that the revised pens, labels and labeling will not exacerbate medication errors.

On March 3, 2008, the Applicant submitted a complete response with revised pen samples, container labels, carton labeling, and Instruction Leaflet.

### 1.3 PRODUCT INFORMATION

Apidra (insulin glulisine [rDNA origin] injection) is a human insulin analog that is a rapid-acting, parenteral blood glucose lowering agent. Apidra is indicated for the treatment of adult patients with diabetes mellitus for the control of hyperglycemia. Apidra has a more rapid onset of action and a shorter duration of action than regular human insulin. Apidra should normally be used in regimens that include a longer-acting insulin or basal insulin analog. Apidra should be given within 15 minutes before a meal or within 20 minutes after starting a meal. Apidra is intended for subcutaneous administration and for use by external infusion pump. The dosage of Apidra should be individualized and determined based on the physician’s advice in accordance with the needs of the patient. Apidra SoloStar will be available as a 3 mL prefilled pen.

## 2 METHODS AND MATERIALS

This section describes the methods and materials used by the Division of Medication Error Prevention staff to conduct a label, labeling, and/or packaging risk assessment. The primary focus of the assessments is to identify and remedy potential sources of medication error prior to drug approval. We define a medication error as any preventable event that may cause or lead to inappropriate medication use or patient harm while the medication is in the control of the health care professional, patient, or consumer.<sup>1</sup>

The label and labeling of a drug product are the primary means by which practitioners and patients (depending on configuration) interact with the pharmaceutical product. The container labels and carton labeling communicate critical information including proprietary and established name, strength, form, container quantity, expiration, and so on.

Given the critical role that the label and labeling has in the safe use of drug products, it is not surprising that 33 percent of medication errors reported to the USP-ISMP Medication Error

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<sup>1</sup> National Coordinating Council for Medication Error Reporting and Prevention. <http://www.nccmerp.org/aboutMedErrors.html>. Last accessed 10/11/2007.

Reporting Program may be attributed to the packaging and labeling of drug products, including 30 percent of fatal errors.<sup>2</sup>

Because our staff analyze reported misuse of drugs, our staff are able to use this experience to identify potential errors with all medication similarly packaged, labeled or prescribed. We use Failure Mode and Effects Analysis (FMEA) and the principles of human factors to identify potential sources of error with the proposed product labels and insert labeling, and provided recommendations that aim at reducing the risk of medication errors.

For this complete response, the Applicant submitted on March 3, 2008 the following pens, labels and labeling for evaluation (see Appendix A, B, C, D for images):

- Apidra SoloStar Container
- Apidra SoloStar Carton
- Lantus SoloStar Container
- Lantus SoloStar Carton
- Instruction Leaflet (no image)
- Apidra SoloStar Pen (product sample)
- Lantus SoloStar Pen (product sample)

We also reviewed the deficiencies outlined in the January 18, 2008 approvable letter and OSE Review #2007-2373 dated January 7, 2008.

### 3 RESULTS

The Applicant has addressed some of the areas in the first deficiency cited in the Approval Letter dated January 18, 2008 which is “Lack of adequate differentiation between Lantus SoloStar and Apidra SoloStar.” However, the Applicant did not address the following specific areas of the deficiency:

- [REDACTED] (b) (4)
- [REDACTED] (b) (4)
- Conducting [REDACTED] (b) (4) studies to provide the Agency with reasonable assurance that the revised pens, labels and labeling will not exacerbate medication errors.

To help further differentiate the product from Apidra SoloStar once Apidra SoloStar is approved, the Applicant did the following:

[REDACTED] (b) (4)

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<sup>2</sup> Institute of Medicine. Preventing Medication Errors. The National Academies Press: Washington DC. 2006. p275.

(b) (4)

The Applicant addressed the second deficiency by proposing to add the following statement in the Instruction Leaflet to address the plunger issue: “Each pen can deliver multiple doses. The pen plunger moves with each dose. The plunger will only move to the end of the cartridge when 300 units of insulin have been given.”

(b) (4)

#### **4 DISCUSSION**

(b) (4)

. However, only the labels and labeling were revised.

Although we acknowledge that the revised labels appear to provide more adequate differentiation from Lantus SoloStar labels in isolation than the previously submitted labels, it is unclear if these changes will adequately differentiate the pens given that the Applicant has not revised the color scheme of the pen body. There are numerous reports of postmarketing errors of confusion with insulin pens which have been described in OSE Review #2007-2373. The Applicant has not provided the Agency with data from studies to support that the revised color scheme provides adequate differentiation from Lantus SoloStar despite the fact that this was recommended in the approval letter dated January 17, 2008. We were provided with data in the complete response dated September 14, 2007 that indicated a significant percentage of color-blinded respondents could not perceive the pens as different or perceive the correct colors. Thus, it remains unclear to us if the proposed labels and labeling changes adequately address the concerns we outlined in the approvable letter.

Lastly, we find the proposed statement in the *Instruction Leaflet* regarding the plunger acceptable.

## 5 CONCLUSIONS AND RECOMMENDATIONS

The Label and Labeling Risk Assessment findings indicate that the presentation of information and design of the proposed container labels, carton labeling, and Instruction Leaflet introduces vulnerability to confusion that could lead to medication errors. We believe these risks identified can be addressed and mitigated prior to drug approval, and provide recommendations in Section 5.2 that aim at reducing the risk of medication errors.

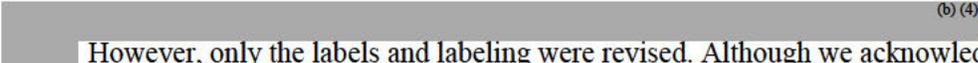
### 5.1 COMMENTS TO THE DIVISION

Based upon our assessment of the complete response, labels, and labeling, the Division of Medication Error Prevention does not believe the Applicant fully addressed the deficiencies cited in the Approvable Letter dated January 18, 2008. We have provided recommendations in Section 5.2 and request this information be forwarded to the Applicant.

We would appreciate feedback on the final outcome of this review. Please copy us on any communication to the Applicant with regard to this review. We would be willing to meet with the Division for further discussion, if needed. If you have further questions or need clarifications, please contact Cheryl Campbell, Project Manager, at 301-796-0723.

### 5.2 COMMENTS TO THE APPLICANT

Based upon our assessment of the complete response, labels, and labeling, the Division of Medication Error Prevention does not believe the Applicant adequately addressed the deficiencies cited in the Approvable Letter dated January 18, 2008. We have identified the following areas of improvement.

1.  (b) (4)
2.  (b) (4)  
However, only the labels and labeling were revised. Although we acknowledge that the revised labels appear to provide better differentiation from Lantus SoloStar labels than the previously submitted labels, we believe they are inadequate to ensure that Apidra SoloStar and Lantus SoloStar pens will not be confused for one another, especially given numerous reports of postmarketing errors of confusion with insulin pens. The Applicant has not provided the Agency with data from studies to support that the revised color scheme provides adequate differentiation from Lantus SoloStar despite the fact that this

was recommended in the approval letter dated January 17, 2008. We were provided with data in the complete response dated September 14, 2007 that indicated a significant percentage of color-blinded respondents could not perceive the pens as different or perceive the correct colors. Thus, it remains unclear to us if the proposed labels and labeling changes adequately address the concerns we outlined in the approvable letter.

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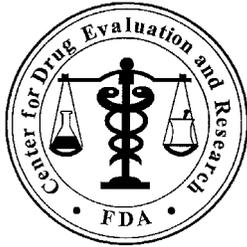
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/s/  
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Judy Park  
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Kellie Taylor  
6/10/2008 03:50:03 PM  
DRUG SAFETY OFFICE REVIEWER

Carol Holquist  
6/10/2008 03:59:46 PM  
DRUG SAFETY OFFICE REVIEWER



**Department of Health and Human Services  
Public Health Service  
Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Surveillance and Epidemiology**

Date: January 4, 2007

To: Mary Parks, MD, Director  
Division of Metabolic and Endocrinology Products

Thru: Denise Toyer, PharmD, Deputy Director  
Carol Holquist, RPh, Director  
Division of Medication Errors and Technical Support

From: Judy Park, PharmD, Safety Evaluator  
Kellie Taylor, PharmD, MPH, Team Leader  
Division of Medication Errors and Technical Support

Subject: Labeling Review

Drug Name: Apidra SoloStar (Insulin Glulisine [rDNA origin] Injection)

Submission Number: S-008

Application Type/Number: NDA 21-629

Applicant/sponsor: Sanofi-Aventis

OSE RCM #: 2007-2373

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## EXECUTIVE SUMMARY

DMETS reviewed the proposed name, product design, container label, carton and insert labeling, (b) (4) (b) (4) for Apidra SoloStar (Insulin Glulisine [rDNA origin] Injection) and identified several areas that contribute to medication errors.

The Label and Labeling Risk Assessment findings indicate that the presentation of information and design of the proposed pen, container and carton labels introduces vulnerability to confusion that could lead to medication errors. DMETS is concerned that Apidra SoloStar may be confused with Lantus SoloStar which has similar packaging and color presentation as the proposed product. The Agency has received numerous reports of confusion between the Lantus and Apidra (b) (4) (b) (4). The root cause analysis of the medication errors has consistently indicated that the errors are the result of similar packaging and color presentation. (b) (4)

The Risk Assessment also determined that the proposed tradename, Apidra SoloStar, may be a source of error and the shared used of “SoloStar” in the proprietary names may inadvertently exacerbate the existing confusion with Apidra and Lantus products. Based on these risks, DMETS concludes that the current submission has not adequately addressed the labeling concerns (i.e. Question E) expressed in the April 25, 2007 approvable letter. (b) (4)

## 1 BACKGROUND

### 1.1 INTRODUCTION

This consult was written in response to a request from the Division of Metabolic and Endocrinology Products to evaluate the product design, container label, carton and insert labeling to identify areas that could lead to medication errors.

### 1.2 REGULATORY HISTORY

The sponsor submitted a Supplemental NDA on April 21, 2006 for the addition of Apidra SoloStar (NDA 21-629/S-008) and Lantus SoloStar (NDA 21-081/S-024), disposable insulin injector pens to their product line. Both supplements received an “approvable” letter on August 24, 2006 citing stability, device, and labeling deficiencies. Subsequently Lantus SoloStar received an “approval” action on April 25, 2007. On September 14, 2007, the sponsor submitted a complete response to the remainder of the questions relating to Apidra SoloStar that were posed in the August 24, 2006 approvable letter.

DMETS reviewed the labels and labeling for Apidra in the OSE reviews listed below.

- OSE Review #03-0180, Proprietary Name and Labeling Review for Apidra, August 29, 2003.
- OSE Review #03-0180-1, Labeling Review for Apidra, December 15, 2003.
- OSE Reviews #03-0180-3, Proprietary Name Review for Apidra, March 19, 2004.
- OSE Review #03-0180-4, Labeling Review, December 2, 2004 for Apidra.
- OSE Review #05-0284 and 05-0285, Labeling Review for Apidra, November 9, 2005.

- OSE Review #06-0106 and 06-0179, Proprietary Name and Labeling Review for Lantus SoloStar and Apidra SoloStar, August 24, 2006.
- OSE Review #2006-853, Proprietary name and Labeling Review for Lantus SoloStar, February 2, 2007.

DMETS previously reviewed the proposed name, Apidra SoloStar, in the OSE Review #06-0106 and 06-0179, dated August 24, 2006. (b) (4)

### 1.3 PRODUCT INFORMATION

Apidra (insulin glulisine [rDNA origin] injection) is a human insulin analog that is a rapid-acting, parenteral blood glucose lowering agent. Apidra is indicated for the treatment of adult patients with diabetes mellitus for the control of hyperglycemia. Apidra has a more rapid onset of action and a shorter duration of action than regular human insulin. Apidra should normally be used in regimens that include a longer-acting insulin or basal insulin analog. Apidra should be given within 15 minutes before a meal or within 20 minutes after starting a meal. Apidra is intended for subcutaneous administration and for use by external infusion pump. The dosage of Apidra should be individualized and determined based on the physician's advice in accordance with the needs of the patient. Apidra SoloStar will be available as a 3 mL prefilled pen.

## 2 METHODS AND MATERIALS

### 2.1 PROPOSED LABELING

This section describes the methods and materials used by DMETS medication error staff to conduct a label, labeling, and/or packaging risk assessment (see 2.2 Container, Carton Label, and Insert Label Risk Assessment). The primary focus of the assessments is to identify and remedy potential sources of medication error prior to drug approval. DMETS defines a medication error as any preventable event that may cause or lead to inappropriate medication use or patient harm while the medication is in the control of the health care professional, patient, or consumer.<sup>1</sup>

The label and labeling of a drug product are the primary means by which practitioners and patients (depending on configuration) interact with the pharmaceutical product. The carton and container labels communicate critical information including proprietary and established name, strength, form, container quantity, expiration, and so on. The insert labeling is intended to communicate to practitioners all information relevant to the approved uses of the drug, including the correct dosing and administration.

Given the critical role that the label and labeling has in the safe use of drug products, it is not surprising that 33 percent of medication errors reported to the USP-ISMP Medication Error Reporting Program may be attributed to the packaging and labeling of drug products, including 30 percent of fatal errors.<sup>2</sup>

Because DMETS staff analyze reported misuse of drugs, DMETS staff are able to use this experience to identify potential errors with all medication similarly packaged, labeled or prescribed. DMETS uses Failure Mode and Effects Analysis (FMEA) and the principles of human factors to identify potential sources of error with the proposed product labels and insert labeling, and provided recommendations that aim at reducing the risk of medication errors.

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<sup>1</sup> National Coordinating Council for Medication Error Reporting and Prevention. <http://www.nccmerp.org/aboutMedErrors.html>. Last accessed 10/11/2007.

<sup>2</sup> Institute of Medicine. Preventing Medication Errors. The National Academies Press: Washington DC. 2006. p275.

For this product the Sponsor submitted on September 14, 2007 the following labels and insert labeling for DMETS review (see Appendices A and B for images):

- Container: 20 mg, 40 mg, 60 mg, 80 mg
- Carton: 20 mg (11 tablet package); 60 mg (7 tablet package)
- Prescribing Information (no image)
- Patient Information for vial and pen (no image)
- Instruction Leaflet for Apidra SoloStar (no image)

(b)  
(4)



### 2.3 MEDICATION ERROR CASES

DMETS searched FDA Adverse Event Reporting System (AERS) database to identify post-marketing reports of medication errors associated with Apidra and Lantus SoloStar. AERS was searched using the tradename “Apidra,” active ingredient “insulin glulisine,” and verbatim term “Lantus Solo%”. The MedDRA Higher Level Group Term (HLGT) “Medication Errors” and Preferred Term (PT) “Pharmaceutical Product Complaint” were used to perform the searches. The AERS search was limited to cases from May 9, 2006 (for Apidra) and January 19, 2007 (for Lantus) to avoid duplicating the results from the previous reviews (OSE reviews #06-0106 and 06-0179 dated August 24, 2006 and #2006-853 dated February 2, 2007).

## 3 RESULTS

### 3.1 PROPOSED LABELING

The color presentation of the proposed pen device, container and carton labels are the same as previously reviewed in OSE reviews #06-0106 and 06-0179. Thus, our concerns with these aspects were noted in our previous reviews.

There is no information in the *Instruction Leaflet* that the plunger of the pen will not move down to the end of the barrel after administration, unlike regular syringes.

(b)  
(4)



### 3.3 MEDICATION ERROR CASES

The AERS search strategy retrieved a total of 42 cases for Apidra and 2 cases for Lantus SoloStar on December 18, 2007.

Out of 42 cases for Apidra, 22 cases pertained to confusion between Apidra and Lantus while the remaining 20 cases were not evaluated further because they were deemed not relevant to this labeling review. In most of the cases pertaining to confusion between Apidra and Lantus, the patients were on both drugs and inadvertently administered one drug instead of the other due to the similar packaging of the drugs. One patient (ISR #5399920-3) stated that the packaging for Apidra and Lantus vials is hard to distinguish especially for diabetic patients who have visual problems. Another color-blind patient (ISR #5467740-7) reported that it was difficult for him to distinguish the two OptiClik pen colors (gray and blue) which are the similar colors as Lantus SoloStar and Apidra SoloStar. The confusion was further increased when patients were using the same OptiClik pen to administer both drugs.

One of the two cases involving Lantus SoloStar was reported in ISMP Medication Safety Alert Newsletter<sup>3</sup>. The patient misdosed the pen and injected 3 times (255 units) the prescribed dose (85 units) which resulted in admission to the emergency room. The patient stated the error occurred because the patient thought the plunger in the pen was similar to the plunger in syringes where it drops to the end of the barrel once administered. However, the plunger in the SoloStar pen moves only partially and is designed to show the remaining amount of drug in the pen. The error did not result in permanent harm. The remaining case involving Lantus SoloStar was not evaluated further because it did not involve a medication error.

## 4 DISCUSSION

The results of the Label and Labeling Risk Assessment indicate that the presentation of information and design of the proposed pen, container and carton labels appear to be vulnerable to confusion that could lead to medication errors with Apidra SoloStar. DMETS is concerned that Apidra SoloStar may be confused with Lantus SoloStar, and that Apidra SoloStar may be vulnerable to administration errors if patients are unfamiliar with the mechanics of disposable pen devices. These risks are discussed separately in detail below. DMETS believes the risks we have identified can be addressed and mitigated prior to drug approval, and provides recommendations in Section 6 that aim at reducing the risk of medication errors.

### 4.1 CONFUSION BETWEEN APIDRA SOLOSTAR AND LANTUS SOLOSTAR

DMETS' primary concern is that the Apidra SoloStar device will be confused with Lantus SoloStar. This concern is based on analysis of the existing confusion between Lantus and Apidra products, (b) (4) and the devices provided to the Agency.

<sup>3</sup> Patients Confused by Insulin Pen Design. ISMP Medication Safety Alert; Volume 12, Issue 23; November 15, 2007.

The proposed Apidra SoloStar device has similar packaging and color presentation to the approved Lantus SoloStar. The Agency has received numerous reports of confusion between the Lantus and Apidra, which have been described in previous reviews (OSE reviews #06-0106 and 06-0179, and 2006-853). Root cause analysis of medication errors involving Lantus and Apidra confusion have consistently indicated that the errors are the result of similar packaging and color presentation. (b) (4)

(b) (4) This review identified an additional 22 reports of confusion between Apidra and Lantus further augmenting our concerns regarding the similar packaging and color presentation of the SoloStar product.

Several reports described confusion between Lantus and Apidra that were a consequence of the similar colors of two OptiClik pens (grey and blue). These OptiClik pens have similar color designations to Lantus SoloStar and Apidra SoloStar, and this example may be a good predictor that the colors scheme of the two SoloStar pens are not more adequately differentiated from each other. DMETS envisions that the current color scheme may lead to confusion between Lantus and Apidra, and, due to the similarity in color with the OptiClik pen device, may also lead to confusion with insulin products administered with OptiClik pens.

(b) (4)

Moreover, (b) (4) DMETS has new concern regarding the use of the proposed tradename, Apidra Solostar. DMETS now believes that the shared use of “SoloStar” for the Apidra and Lantus disposable pen products increases the similarity between these products, and may inadvertently exacerbate the existing confusion with the Apidra and Lantus products; particularly in conjunction with the physical and visual similarity of the pen products. (b) (4)

(b) (4) As such, DMETS believes the trademark Apidra SoloStar is vulnerable to confusion with Lantus SoloStar, and may lead to medication errors.

#### 4.2 ADMINISTRATION ERRORS

The postmarketing error of Lantus SoloStar where the patient administered the drug three times because the plunger did not move down to the end of the barrel may be due to lack of education and familiarity with the SoloStar pen. This risk may be greater if the patients are used to administering Lantus or Apidra vials via syringe.

## 5 CONCLUSIONS

The Label and Labeling Risk Assessment findings indicate that the presentation of information and design of the proposed pen, container and carton labels introduces vulnerability to confusion that could lead to medication errors. The Risk Assessment also determined that the proposed tradename, Apidra SoloStar, may be a source of error and inadvertently exacerbate the existing confusion with Apidra and Lantus products. Based on these risks, DMETS concludes that the current submission has not adequately addressed the labeling concerns (i.e. Question E) expressed in the April 25, 2007 approvable letter.

(b) (4)

Overall, our Risk Assessment is limited by our current understanding of medication errors and causality. The successful application of Failure Modes and Effect Analysis depends upon the learning gained for a spontaneous reporting program. It is quite possible that our understanding of medication error causality would benefit from unreported medication errors; and, that this understanding could have enabled the Staff to identify vulnerability in the proposed name, packaging, and labeling that was not identified in this assessment. To help minimize this limitation in future assessments, we encourage the Sponsor to provide the Agency with medication error reports involving their marketed drug products regardless of adverse event severity.

## 6 RECOMMENDATIONS

6.1 Based on the labeling deficiencies noted in this review, DMETS recommends that the Division not approve the Supplemental NDA (S-008) submitted on April 21, 2006 providing for the addition a disposable Apidra pen device.

6.2

(b) (4)

6.3

(b) (4)

6.4 Include in the *Instruction Leaflet* of Apidra SoloStar a statement that the plunger will not move down to the end of the barrel when the drug is administered (See forthcoming DSRCs review #2007-2373).

### 6.5 *Comments to the Sponsor*

6.5.1

(b) (4)

6.5.2

(b) (4)

6.5.3 Include in the *Instruction Leaflet* of Apidra SoloStar a statement that the plunger will not move down to the end of the barrel when the drug is administered.

## **7 REFERENCES**

### ***1. Adverse Events Reporting System (AERS)***

AERS is a database application in CDER FDA that contains adverse event reports for approved drugs and therapeutic biologics. These reports are submitted to the FDA mostly from the manufactures that have approved products in the U.S. The main utility of a spontaneous reporting system that captures reports from health care professionals and consumers, such as AERS, is to identify potential postmarketing safety issues. There are inherent limitations to the voluntary or spontaneous reporting system, such as underreporting and duplicate reporting; for any given report, there is no certainty that the reported suspect product(s) caused the reported adverse event(s); and raw counts from AERS cannot be used to calculate incidence rates or estimates of drug risk for a particular product or used for comparing risk between products.

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/s/

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Judy Park  
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Kellie Taylor  
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DRUG SAFETY OFFICE REVIEWER

Denise Toyer  
1/4/2008 03:54:38 PM  
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Carol Holquist  
1/4/2008 05:06:17 PM  
DRUG SAFETY OFFICE REVIEWER



**Department of Health and Human Services  
Public Health Service  
Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Surveillance and Epidemiology**

Date: January 4, 2007

To: Mary Parks, M.D., Director  
Division of Metabolism and Endocrinology  
Products

Through: Jodi Duckhorn, M.A., Team Leader  
Patient Labeling and Education Team  
Office of Surveillance and Epidemiology

From: Sharon R. Mills, BSN, RN, CCRP  
Patient Product Information Specialist  
Patient Labeling and Education Team  
Office of Surveillance and Epidemiology

Subject: OSE review of Patient Labeling

Drug Name(s): Apidra (Insulin glulisine [rDNA origin] injection)

Application Type/Number: NDA 21-629

Submission Number: S-008

Applicant/sponsor: Sanofi Aventis

OSE RCM #: 2007-2373

## INTRODUCTION

Sanofi Aventis received original approval of its New Drug Application, NDA 21-62, for Apidra (insulin glulisine [rDNA origin] injection) on April 16, 2004, for the treatment of adult patients with diabetes mellitus for the control of hyperglycemia. Apidra currently has two approved product presentations, vial and 3 ml cartridge system (300 units per cartridge system) 100 units per mL (U-00) for use with the OptiClik insulin pen.

Aventis submitted a Supplemental New Drug Application (NDA 21-629/S-008 on April 24, 2006, for the addition of Apidra SoloStar, a new disposable insulin pen injector. The Agency issued an approvable letter on August 24, 2006 for Lantus SoloStar (NDA 21-081/S-024) and Apidra SoloStar (NDA 21-629/S-008) citing stability, device and labeling deficiencies. The sponsor submitted a complete response to approvable letter addressing the deficiencies for Lantus SoloStar, and notified the Agency of their intent to file an amendment to NDA21-081/S-024, on October 24, 2006. The amended supplement was approved by the Agency on April 25, 2007. On September 14, 2007 Sanofi Aventis submitted a complete response to approvable letter for Apidra SoloStar, addressing the deficiencies previously cited. The sponsor indicated that questions 2-8 listed in the approvable letter for both Lantus SoloStar and Apidra SoloStar are device-related and not product specific, and were addressed by the sponsor in the complete response submitted for Lantus SoloStra on October 24, 2006.

OSE previously reviewed the Patient Labeling for Apidra on the following dates: January 15, 2003, April 8, 2004, and May 31, 2007. OSE was requested to review the Patient Labeling in the form of a PPI and Instruction Leaflet, for the Apidra Solostar 3 mL disposable insulin delivery device, submitted with this supplement.

Please see the separate labeling review by DMETS, which includes a review of medication errors and the Instruction leaflet.

## MATERIAL REVIEWED

The proposed PI submitted on September 14, 2007 was reviewed along with the proposed Patient Package Insert (PPI) and Instruction Leaflet submitted on the same date.

## DISCUSSION

See the attached document for our recommended changes to the proposed Instruction leaflet. Our recommended changes are consistent with current research to improve risk communication to a broad range of audiences including those with lower levels of literacy.

We refer to Apidra SoloStar as the Apidra pen throughout this review.

(b) (4)

Comments to the review division are ***bolded, italicized and underlined.***

## CONCLUSIONS AND RECOMMENDATIONS

- The proposed PPI submitted by the sponsor with this submission has a Flesch Kincaid Grade Level of 9.4 and a Flesch Kincaid Reading Ease Score of 50.1. To enhance

comprehension, patient materials should be written at a 6<sup>th</sup> to 8<sup>th</sup> grade reading level and have a reading ease score of at least 60 % (60% corresponds to an 8<sup>th</sup> grade reading level).

- The sponsor currently has two approved PPIs for Apidra, one for the vial presentation and one for the 3 ml cartridge system (300 units per cartridge system) 100 units per mL (U-00) for use with the OptiClik insulin pen.
- We continue to recommend that the sponsor merge the multiple product PPIs (one for each packaging configuration) into **one** PPI for Apidra. A PPI, like a PI is for the product, not for the packaging configuration (vial, cartridge, pen, etc.). Reference all available product packaging configurations in the PPI. Each Apidra presentation should have its own individual Patient Instructions for Use, as recommended for all products with multiple presentations.
- The proposed PPI and currently approved Apidra PPIs have a bullet list at the top of the PPI listing the sections of information contained in the PPI. (b) (4)

[Redacted]

Otherwise, the information is meaningless to patients.

- (b) (4). Keep information on diabetes brief. The purpose of patient information leaflets is to enhance appropriate use of medications and to provide important risk information about medications. (b) (4)  
The Patient Information is derived from and must be consistent with the PI.

- Multiple pen devices concurrently exist in the marketplace. Patients may use one or more pen devices or switch between pen devices. For this reason, it is important to help patients to distinguish an important difference that may exist in using the Apidra pen versus another pen on the market. The plunger does not move all the way to the end of the insulin reservoir when an injection is given. To avoid patient misinterpretation that the dose of Apidra was not given or not fully given, we recommend adding the following language to the *Information for Patients* subsection of the *Warnings* section in the PI, and Step 1. Check the insulin in the Apidra pen Instruction leaflet:

- [Redacted] (b) (4)

- Add statements to the PPI and Instruction leaflet telling patients:

- [Redacted] (b) (4)

- [REDACTED] (b) (4)
- [REDACTED] (b) (4)
- Our review of the Instruction leaflet is limited to review for consistency with the PPI and PI, and for readability. We defer to DMETS to review the Instruction leaflet related to potential for Medication Errors related to the Apidra pen.
- The proposed Patient Instruction leaflet has a Flesch Kincaid Grade Level of 10.6 and a Flesch Kincaid Reading Ease Score of 52.4. The sponsor should simplify the instructions and ensure that they are written at or less than an 8<sup>th</sup> grade reading level.
- The section of the PPI entitled [REDACTED] (b) (4) should be moved to the Instruction leaflet, since it is specific to the product presentation. The section [REDACTED] (b) (4) refers patients to [REDACTED] (b) (4) section for additional information. Since we recommend one PPI for the product and individual Patient Instructions for Use for each presentation, this sentence should be revised to say, for example, [REDACTED] (b) (4)
- We continue to note that existing PPIs for diabetic products are quite varied and most are written at a reading comprehension level that is too high to be understood by low literacy readers. The review division may want to consider initiating class PPI labeling in the future for diabetic products utilizing the following suggestions previously provided in the OSE consult for Apidra dated January 15, 2003:
  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 6<sup>th</sup> to 8<sup>th</sup> grade reading comprehension level is optimal of 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 according to DDMAC guidelines.

We will provide the review division with clean and marked up copies of our revisions to the Patient Instruction leaflet in Word. We recommend using the clean copy as the working document.

Please let us know if you have any questions.

15 Page(s) of Draft Labeling has been Withheld in Full as b4 (CCI/TS) immediately following this page

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/s/

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Sharon Mills  
1/4/2008 03:54:15 PM  
DRUG SAFETY OFFICE REVIEWER

Jodi Duckhorn  
1/4/2008 03:58:02 PM  
CSO



## DEPARTMENT OF HEALTH AND HUMAN SERVICES

## MEMORANDUM

Food and Drug Administration  
Office of Device Evaluation  
9200 Corporate Avenue  
Rockville, MD 20850

**Date:** July 10, 2006

**From:** Biomedical Engineer  
DAGID/GHDB, HFZ-480

**Subject:** NDA 21-081/S024  
Company Name: Sanofi-Aventis  
Device: Lantus SoloStar (insulin glargine [rDNA origin])  
Indications for Use: To treat adult and pediatric patients with type 1 diabetes or adult patients with type 2 diabetes

NDA 21-629/S008  
Company Name: Sanofi-Aventis  
Device: Apidra SoloStar (insulin glulisine [rDNA origin])  
Indications for Use: For treatment of adult patients with diabetes mellitus for the control of hyperglycemia

**To:** Dr. Janice Brown, CDER/OPS/ONDQA/DPE, HFD-510

**Thru:** Branch Chief, Anthony Watson *ACC For ABW*

#### 1.0 Background

This consult review was requested for the disposable insulin pen, SoloStar. The requesting reviewer has asked that I focus on the accuracy and precision of the device and the information provided in section 3.2.P.7 for the container closure system which includes device components, specifications, methods, and assembly process description. The same SoloStar device is being used for two separate NDA applications which are both being addressed in this review.

The SoloStar injection system is a device that provides a method of accurately injecting a selected dose of insulin through a single lumen hypodermic needle. The device is intended to be used for self-injection by patients. Patients who are not able to handle the device properly (according to Health Care Professional's assessment) require assistance from a third person. The device is disposable and cannot be reused. The device does not contain electronic components. The device has a pen cap for safety and to protect the cartridge.

The dose is pre-selected by rotating a dosage selector at the rear end of the device. The number of selected insulin units is displayed in the dose window on the side of the pen. The dialing mechanism allows dosage in 1 insulin unit increments. It provides a maximum of 80 insulin units in one dosing. The total content of the cartridge is 300 insulin units. Before the injection, a pen injector needle is mounted onto the front end of the device and inserted under the skin. The dose is delivered by pressing the injection button.

The SoloStar cartridge holder into which the 3mL cartridge is irreversibly attached, is considered secondary packaging. No part of the SoloStar has contact with the drug product. The SoloStar device does not influence the container closure integrity or stability of the insulin. Therefore, the shelf-life and storage directions of the SoloStar are the same as the approved cartridges (i.e., 24 months at 2-8°C). All plastic parts that could come into skin contact during use have been tested for skin sensitivity according to (b) (4)

## **2.0 Review**

The SoloStar was tested according to ISO 11608-1:2000 "Pen injectors for medical use – Part 1: Pen injectors – Requirements and test methods". The cartridge in conjunction with the SoloStar was assessed according to ISO 11608-3:2000 "Pen injectors for medical use – Part 3: Finished cartridges – Requirements and test methods" and (b) (4). The sponsor performed the following tests:

- Functional inspection (visual, audible, tactile)
- Dose accuracy (ambient, cool atmosphere, hot atmosphere, cold storage atmosphere, dry heat atmosphere)
- Free fall (dose accuracy, visual inspection, functional inspection)

The sponsor has indicated that the dose accuracy of the device is (b) (4). ISO 11608-1 specifies that single-compartment cartridge doses less than 200µL should have an absolute error not exceeding 10µL and single-compartment cartridge doses greater than 200µL should have a dose accuracy not exceeding 5%. Therefore, the sponsor's dose accuracy specification meets the requirements of ISO 11608-1.

The sponsor adequately described the assembly process of the mechanism subassembly and cap and cartridge holder subassembly.

## **3.0 Correspondence**

The submission that Sanofi submitted described a device with no electrical components. However, the sample provided by the company had an LCD for dose setting. On June 20, 2006, I called Mr. Kevin Malobisky to determine which device the company intended to submit. Mr. Malobisky indicated that I had the sample of the OptiClick and not the SoloStar.

## **4.0 Comments**

1. Please provide a copy of the SoloStar Instructions for Use.
2. Please describe the method by which the SoloStar indicates that the injection has been completed.
3. You have indicated that the dialing mechanism allows dosage in 1 insulin unit increments and provides a maximum of 80 insulin units in one dosing. Please describe how the design limits dosing to 80 units. Please describe the testing that has been conducted on the dose setting mechanism. Specifically, has testing been performed to assess functionality if the user rapidly turns the dial or if the user turns the dial clockwise past 80 units and then attempts to turn the dial counterclockwise.
4. Please describe the method and mechanism for ensuring that the last dose delivered from the insulin cartridge satisfies requirements for dose accuracy.
5. Please indicate whether the device has a safety mechanism to prevent accidental firing.
6. Please identify the pen injector needles that are compatible with the SoloStar in your Instructions for Use.
7. You state that the dose is delivered by pressing the injection button until it is in its original end position. Please clarify what is meant by this statement.
8. There is no indication in the submission that user testing has been performed for this device. The number of steps involved in performing a successful injection with this device could lead to user errors and potential life threatening situations. You should perform a risk analysis to identify the device use tasks that could lead to patient safety issues and then conduct user testing to identify and test mitigation measures that adequately reduce the risk of patient injury. Potential problems such as overdosing, underdosing, or misdosing can result from a variety of user-related tasks such as improper use of the dialing mechanism, failure to properly attach the needle, etc. User testing should be performed to determine and mitigate all potential use-related issues. Without results from usability testing leading to mitigation of hazards and changes in system requirements, it is not possible to determine whether the future marketed device will be safe and effective. Please provide a test plan and test results for usability testing for the new device. We recommend that you consult the following guidance documents for information about acceptable usability testing:

- Do it By Design - An Introduction to Human Factors in Medical Devices  
<http://www.fda.gov/cdrh/humfac/doi/pdf>
- Medical Device Use-Safety: Incorporating Human Factors Engineering into Risk Management  
<http://www.fda.gov/cdrh/humfac/1497.pdf>

**5.0 Recommendation**

REQUEST ADDITIONAL INFORMATION

  
Jason Lipman

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/s/

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Janice Brown  
8/15/2006 08:51:33 AM  
CHEMIST

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*  
**NDA 021629/S-008**

**ADMINISTRATIVE and CORRESPONDENCE**  
**DOCUMENTS**

**Hartford, Rachel**

---

**From:** Hartford, Rachel  
**Sent:** Friday, January 16, 2009 3:54 PM  
**To:** 'Rima.Nassar@sanofi-aventis.com'  
**Subject:** RE: Proposal for Apidra SoloStar  
**Follow Up Flag:** Follow up  
**Flag Status:** Purple

Rima,

We are unable to take the action you propose for the SoloStar Supplement with the previously submitted labeling. Please accept the edits you agree with, and make any new revisions in tracked changes for the PPI and PIFUs I sent via email on January 15, 2009. Email the WORD documents with your revisions to me. There should also be changes to the PI; include a marked-up WORD document for it in your email too.

Thank you,

Rachel

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**From:** Rima.Nassar@sanofi-aventis.com [mailto:Rima.Nassar@sanofi-aventis.com]  
**Sent:** Friday, January 16, 2009 1:53 PM  
**To:** Hartford, Rachel  
**Subject:** Proposal for Apidra SoloStar

Dear Rachel,

This is in reference to the comments/feedback received from the Agency on January 15, 2009 for the following Apidra labeling components:

- Patient Information (PPI)
- Patient Instructions for Use for 10 mL vial (PIFU-vial)
- Patient Instructions for Use for 3 mL cartridge system (PIFU-cartridge system)
- Patient Instructions for Use for SoloStar (PIFU-SoloStar)

We reviewed the labeling components and have the following comments:

- We acknowledge the Agency's proposal to sanofi-aventis to defer submission of additional figures to a later date in a Prior Approval Supplement, and we agree with this proposal as this would allow us more time to design additional figures, improve existing ones, complete the artwork, and incorporate in the Patient Instructions for Use.
-  (b) (4)
- The revisions proposed by DRISK for the PPI, PIFU-vial, PIFU-cartridge system, and PIFU-SoloStar are mainly editorial in nature. We are willing to accept these changes, and in some cases, propose alternative text to further improve readability and to make wording consistent among the vial, cartridge system and

3/9/2009

SoloStar.

Based on the above, sanofi-aventis proposes the following:

- We will combine all the editorial changes for the PPI, PIFU-vial, PIFU-cartridge system, and PIFU-SoloStar together with new and improved figures for Apidra in one Prior Approval Supplement.
-  (b) (4)
- We commit to submit the (b) (4) Prior Approval Supplements for Apidra  (b) (4) in a timely manner and the latest by March 31, 2009.

Accordingly, we request that the Agency grant us approval for Apidra SoloStar based on the labeling components previously submitted on November 10, 2008 for the Prescribing Information, and August 19, 2008 for the Patient Information, Patient Instructions for Use for the 10 mL vial, Patient Instructions for Use for the 3 mL cartridge system, and the Instruction Leaflet for Apidra SoloStar.

We wish to thank the Agency for their thorough review of Apidra SoloStar and look forward to a prompt and favorable response to our proposal. We would also welcome an opportunity to meet with the Agency at your earliest convenience to further discuss our proposal and reach a mutual agreement.

Best regards,

Rima

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Rima B. Nassar, Ph.D.  
Global Diabetes Axis Head  
Corporate Regulatory Affairs  
Tel: 908-304-6471

 (b) (6)  
E-Mail: Rima.Nassar@sanofi-aventis.com

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/s/

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Rachel E Hartford  
3/16/2009 08:58:46 PM  
CSO

## Hartford, Rachel

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**From:** Hartford, Rachel  
**Sent:** Wednesday, July 30, 2008 11:37 AM  
**To:** 'Rima.Nassar@sanofi-aventis.com'  
**Subject:** NDA 21-629/S008 Apidra SoloStar- August 6, 2008 Preliminary Meeting Minutes

**Attachments:** NDA 21-629\_S008 2nd Prelim Mtg Mins.pdf

Rima,

The preliminary meeting minutes for our August 6, 2008, meeting are attached. I will be in the office all afternoon; please call if you have questions.

Thank you,

Rachel



NDA 21-629\_S008  
2nd Prelim Mtg...

*Rachel E. Hartford*

**Regulatory Project Manager**

**Division of Metabolism and Endocrinology Products**

**Center for Drug Evaluation and Research**

**Food and Drug Administration**

**[rachel.hartford@fda.hhs.gov](mailto:rachel.hartford@fda.hhs.gov)**

**301-796-0331 (phone)**

**301-796-9712 (fax)**

**Meeting Type: C**

**Meeting Category: Guidance Meeting**

**Application Number: NDA 21-629/S-008**

**Product Name: Apidra (insulin glulisine [rDNA origin] injection)**

**Sponsor: sanofi-aventis**

**Meeting Date: Scheduled for Wednesday, August 6, 2008**

**Meeting Time: 3:00 - 4:00 pm**

**Meeting Format: Videoconference**

**Meeting Recorder: Rachel Hartford**

*This material consists of our preliminary responses in preparation for the discussion at the meeting scheduled for Wednesday, August 6, 2008, between sanofi-aventis, the Division of Metabolism and Endocrinology Products and the Division of Medication Error Prevention and Analysis (DMEPA).*

*This material is shared to promote a collaborative and successful discussion at the meeting. The minutes of the meeting will reflect agreements, important issues, and any action items discussed during the meeting and may not be identical to these preliminary comments. If these answers and comments are clear to you and you determine that further discussion is not required, you have the option of cancelling the meeting (please contact Rachel Hartford at 301-796-0331). If you determine that discussion is needed, you have the option of reducing the agenda. Note that if there are any major changes to your development plan, the purpose of the meeting, or the issues based on our preliminary responses, we may not be prepared to discuss or reach agreement on such changes at the meeting. Please note there is not sufficient time to prepare a response to any additional submission prior to the meeting.*

## **QUESTIONS**

Your questions are repeated below, followed by our responses in bold.

Question 1: The comments sent by the Agency state that the study should include a poorly differentiated pair of Apidra SoloStar and Lantus SoloStar in parallel with the proposed Apidra SoloStar and currently marketed Lantus SoloStar pens. It is not clear to the sponsor why these poorly differentiated pens should be included in the study or how to design/assemble these pens. Can the Agency provide the sponsor with direction and guidance on the need to include the poorly differentiated pens in the study and on the design/assembly required for these pens?

**FDA Response: The rationale for using a poorly differentiated pair of pens is to provide a baseline rate of selection error. We believe establishing a baseline rate of selection error for two pens that lack differentiation will give context for**

**interpreting the selection errors observed in the parallel study of the proposed Apidra SoloStar pen device.**

**The design of the “Poorly” differentiated SoloStar pens presented in the July 10, 2008, submission is adequate. The Agency has no further guidance to offer on the design/assembly for these pens.**

Question 2: The sponsor has several questions related to the general methodology of the study such as the recommended monadic design and would like to discuss these with the Agency prior to the initiation of the study. Can the Agency provide further clarification to the monadic design recommended for the study?

**FDA Response: The intent of the monadic design (Question 12 of the proposed protocol) is to assess the patient’s ability to correctly identify the SoloStar pens in isolation from one another. We recommend that this aspect be assessed because confirmation bias plays a role in product selection errors. Confirmation bias contributes to medication errors because when selecting products, humans tend to perceive confirming evidence (e.g., color, shapes, font type, symbols, etc.) more readily than disconfirming evidence (e.g., differences in product nomenclature). We note that there are underlying similarities in the proposed Apidra SoloStar pen and the Lantus SoloStar relating to color (blue vs. grey), packaging (pen), symbols (stripe bars), labels (b) (4) which may predispose consumers to confirmation bias and selection errors. Moreover, root cause analysis of medication errors involving currently marketed Apidra and Lantus products (vials, cartridges) suggests that the similar packaging and labeling of the products creates confirmation bias that is contributing to consumer and practitioner selection errors in some cases. Thus, we believe that it is important to assess if subjects can discriminate the two pens from one another in isolation as well as when presented next to each other.**

Question 3: The sponsor would like to discuss the recruiting criteria prior to initiation of the study, as the subject selection may have an impact on the study outcome. Can the Agency provide further clarification on the recruiting criteria for subjects included in the study?

**FDA Response: Recruit approximately 200 individuals with diabetes representative of the potential Apidra SoloStar users. Age, ethnicity, education, literacy, gender, and employment status of the study subjects should be similar to the current users of the Apidra vial or cartridges. (b) (4) some patients should be maintained on oral medication therapy only, and others should be insulin users. The screening questions in the proposed study appear appropriate.**

**Additional Comment: We have reviewed your proposed Pen Color Differentiation Study submitted on July 10, 2008. The study follows the advice in our June 27, 2008, correspondence.**

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/s/

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Rachel E Hartford  
3/16/2009 08:57:04 PM  
CSO

## Hartford, Rachel

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**From:** Hartford, Rachel  
**Sent:** Wednesday, June 04, 2008 5:51 PM  
**To:** 'Richard.Gural@sanofi-aventis.com'  
**Cc:** 'Rima.Nassar@sanofi-aventis.com'  
**Subject:** NDA 21-629/S008 Preliminary Meeting Minutes

**Follow Up Flag:** Follow up  
**Flag Status:** Purple

**Attachments:** Prelim Mtg Mins.doc

Dr Gural,

The preliminary minutes for our June 11, 2008 meeting are attached. Please provide an attendee list so that our security staff has sufficient advance time to prepare temporary visitor badges.

Sincerely,

Rachel Hartford



Prelim Mtg Mins.doc  
(31 KB)

*Rachel E. Hartford*

**Regulatory Project Manager**

**Division of Metabolism and Endocrinology Products**

**Center for Drug Evaluation and Research**

**Food and Drug Administration**

[rachel.hartford@fda.hhs.gov](mailto:rachel.hartford@fda.hhs.gov)

**301-796-0331 (phone)**

**301-796-9712 (fax)**

**Meeting Type: C**

**Meeting Category: Guidance Meeting**

**Application Number: NDA 21-629/S-008**

**Product Name: Apidra (insulin glulisine [rDNA origin] injection)**

**Sponsor: sanofi-aventis**

**Meeting Date: Scheduled for Wednesday, June 11, 2008**

**Meeting Time: 3:00 - 4:00 pm**

**Meeting Format: Face-to-Face**

**Location: White Oak Campus; Silver Spring, MD**

**Meeting Recorder: Rachel Hartford**

*This material consists of our preliminary response in preparation for the discussion at the meeting scheduled for Wednesday, June 11, 2008, between sanofi-aventis, the Division of Metabolism and Endocrinology Products and the Division of Medication Error Prevention.*

*This material is shared to promote a collaborative and successful discussion at the meeting. The minutes of the meeting will reflect agreements, important issues, and any action items discussed during the meeting and may not be identical to these preliminary comments. If these answers and comments are clear to you and you determine that further discussion is not required, you have the option of cancelling the meeting (please contact Rachel Hartford at 301-796-0331). If you determine that discussion is needed, you have the option of reducing the agenda and/or changing the format of the meeting (e.g., from face-to-face to teleconference). Note that if there are any major changes to your development plan, the purpose of the meeting, or the issues based on our preliminary responses, we may not be prepared to discuss or reach agreement on such changes at the meeting. Please note there is not sufficient time to prepare a response to any additional submission prior to the meeting.*

Supplement -008 proposes the addition of the Apidra SoloStar disposable injector pen.

Based upon our assessment of your March 3, 2008, labels, and labeling, FDA does not believe you have adequately addressed the deficiencies cited in the Approvable Letter dated January 18, 2008. We have identified the following area that still needs to be addressed:

The approval letter dated January 18, 2008,

(b) (4)

(b) (4)

We acknowledge that the revised labels appear to provide better differentiation from Lantus SoloStar labels in isolation than the previously submitted labels. However, it remains unclear whether these changes will adequately differentiate the pens given that you did not revise the color scheme of the pen body.

There are numerous reports of errors involving confusion with insulin pens and the Lantus and Apidra products, thus without additional studies to evaluate the impact of the revised labels we do not have reasonable assurance that Apidra SoloStar and Lantus SoloStar pens will not be confused for one another.

Thus, we reiterate our request that you study the adequacy of the revised labels to differentiate the Apidra SoloStar and Lantus SoloStar pens and encourage you to submit a draft study protocol for our review and comment prior to the initiation of the study. (b) (4)

Even (b) (4)  
with more contrasting pen colors, we would encourage you to perform (b) (4) studies to provide reasonable assurance that medication errors are not exacerbated.

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/s/

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Rachel E Hartford  
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CSO

**Hartford, Rachel**

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**From:** Hartford, Rachel  
**Sent:** Thursday, July 31, 2008 6:32 PM  
**To:** 'Rima.Nassar@sanofi-aventis.com'  
**Subject:** RE: NDA 21-629/S008 Apidra SoloStar- August 6, 2008 Preliminary Meeting Minutes  
**Follow Up Flag:** Follow up  
**Flag Status:** Purple

Thanks Rima,

The meeting has been cancelled.

Rachel

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**From:** Rima.Nassar@sanofi-aventis.com [mailto:Rima.Nassar@sanofi-aventis.com]  
**Sent:** Thursday, July 31, 2008 6:30 PM  
**To:** Hartford, Rachel  
**Cc:** Richard.Gural@sanofi-aventis.com; Paul.Jansen@sanofi-aventis.com; Angela.Moskow@sanofi-aventis.com; Joffe, Hylton  
**Subject:** RE: NDA 21-629/S008 Apidra SoloStar- August 6, 2008 Preliminary Meeting Minutes

Dear Rachel,

Thank you very much for promptly sending the feedback/comments from the Agency regarding the proposed color differentiation study between Lantus SoloStar and Apidra SoloStar. Following internal discussions, the team believes that the answers and comments included in your letter are clear to us; no further discussions with the Agency are needed at this time. As the Agency agreed with the submitted study questionnaire and had no comments, we will initiate the study as soon as possible. Accordingly, we wish to cancel the videoconference scheduled for August 6 between representatives from the Agency and sanofi-aventis.

Best regards,  
Rima Nassar

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**From:** Hartford, Rachel [mailto:Rachel.Hartford@fda.hhs.gov]  
**Sent:** Wednesday, July 30, 2008 11:37 AM  
**To:** Nassar, Rima R&D/US  
**Subject:** NDA 21-629/S008 Apidra SoloStar- August 6, 2008 Preliminary Meeting Minutes

Rima,

The preliminary meeting minutes for our August 6, 2008, meeting are attached. I will be in the office all afternoon; please call if you have questions.

Thank you,

Rachel

<<NDA 21-629\_S008 2nd Prelim Mtg Mins.pdf>>

*Rachel E. Hartford*  
**Regulatory Project Manager**  
**Division of Metabolism and Endocrinology Products**

3/9/2009

**Center for Drug Evaluation and Research**

**Food and Drug Administration**

[rachel.hartford@fda.hhs.gov](mailto:rachel.hartford@fda.hhs.gov)

**301-796-0331 (phone)**

**301-796-9712 (fax)**

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/s/

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Rachel E Hartford  
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## Hartford, Rachel

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**From:** Hartford, Rachel  
**Sent:** Friday, January 30, 2009 12:06 PM  
**To:** 'Rima.Nassar@sanofi-aventis.com'  
**Subject:** Apidra SoloStar Labeling

**Follow Up Flag:** Follow up  
**Flag Status:** Purple

**Attachments:** 1.26.09 Apidra - AnnotatedPPI - Jan2009.doc; 1.27.09 Apidra - AnnotatedIFUvial - Jan2009.doc; 1.26.09 Apidra - Annotated IFUcartridge - Jan2009.doc; 1.26.09 Apidra - AnnotatedIFUSoloStar - Jan2009.doc; Apidra - AnnotatedPI - Jan2009.doc

Rima,

We do not have any additional edits to the PI you emailed on 22Jan09. If you have additional edits, please accept the the FDA tracked changes you agree with prior to returning the labeling pieces via email. If you accept all our proposed changes to the PPI and IFUs, formally submit all labeling pieces.

Thanks,

Rachel



1.26.09 Apidra -  
AnnotatedPPI ...



1.27.09 Apidra -  
AnnotatedIFUv...



1.26.09 Apidra -  
Annotated IFU...



1.26.09 Apidra -  
AnnotatedIFUS...

*Rachel E. Hartford*

**Regulatory Project Manager**

**Division of Metabolism and Endocrinology Products**

**Center for Drug Evaluation and Research**

**Food and Drug Administration**

[rachel.hartford@fda.hhs.gov](mailto:rachel.hartford@fda.hhs.gov)

**301-796-0331 (phone)**

**301-796-9712 (fax)**



Apidra -  
notatedPI - Jan2009

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/s/

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Rachel E Hartford  
3/16/2009 08:52:44 PM  
CSO

## Hartford, Rachel

---

**From:** Hartford, Rachel  
**Sent:** Thursday, January 15, 2009 9:43 AM  
**To:** 'Rima.Nassar@sanofi-aventis.com'  
**Subject:** Apidra SoloStar

**Follow Up Flag:** Follow up  
**Flag Status:** Purple

**Attachments:** APIDRA PPI DRISK 1-2009 marked up copy.doc; APIDRA SoloStar Prefilled Pen IFU DRISK 1-2009 maked up copy.doc; APIDRA 10 mL vial IFU DRISK 1-2009 marked-up copy.doc; APIDRA 3 mL cartridge IFU DRISK 1-2009 marked up copy.doc

Good Morning Rima,

Please review the attached labeling, accept all edits that you agree with, and send in any new revisions in tracked changes. As we discussed yesterday additional figures are needed. Confirm that you agree to submit a Prior Approval Supplement in response to our Supplement request letter for additional figures. Also, propose a timeline for when the labeling pieces with figures will be submitted.

Sincerely,

Rachel



APIDRA PPI DRISK 1-2009 marked... APIDRA SoloStar Prefilled Pen ... APIDRA 10 mL vial IFU DRISK 1-... APIDRA 3 mL cartridge IFU DRIS..

*Rachel E. Hartford*

**Regulatory Project Manager**

**Division of Metabolism and Endocrinology Products**

**Center for Drug Evaluation and Research**

**Food and Drug Administration**

[rachel.hartford@fda.hhs.gov](mailto:rachel.hartford@fda.hhs.gov)

**301-796-0331 (phone)**

**301-796-9712 (fax)**

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/s/

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Rachel E Hartford  
3/16/2009 08:50:39 PM  
CSO

## Hartford, Rachel

---

**From:** Hartford, Rachel  
**Sent:** Tuesday, February 10, 2009 1:07 PM  
**To:** 'Rima.Nassar@sanofi-aventis.com'  
**Subject:** Lantus PI & Apidra SoloStar

**Follow Up Flag:** Follow up  
**Flag Status:** Purple

**Attachments:** annotated\_pi\_09Feb09.doc

Rima,

Please accept all FDA tracked changes you agree with in the attached Lantus PI. Use track changes for any additional edits you make. Please return the PI via email by COB 18Feb09; let me know if you need additional time.

Thanks,

Rachel



annotated\_pi\_09Feb09.doc (1 MB...)

P.S. I just spoke with Hylton. He asked me to let you and Richard know that we plan to issue the action letter for Apidra SoloStar during the week of February 16-20. I will gladly send you a pdf of the action letter so you don't have to wait for the mail.

*Rachel E. Hartford*

**Regulatory Project Manager**  
**Division of Metabolism and Endocrinology Products**  
**Center for Drug Evaluation and Research**  
**Food and Drug Administration**  
[rachel.hartford@fda.hhs.gov](mailto:rachel.hartford@fda.hhs.gov)  
**301-796-0331 (phone)**  
**301-796-9712 (fax)**

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/s/

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Rachel E Hartford  
3/16/2009 08:49:04 PM  
CSO

## Hartford, Rachel

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**From:** Hartford, Rachel  
**Sent:** Monday, March 17, 2008 1:10 PM  
**To:** 'Rima.Nassar@sanofi-aventis.com'  
**Subject:** FW: Apidra SoloStar NDA 21-629/S008 Complete Response Consult Request

**Follow Up Flag:** Follow up  
**Flag Status:** Purple

Rima,

Your March 3, 2008, Complete Response submission addresses the deficiencies outlined in our January 18, 2008 Approvable Letter and as such is considered a Complete Response. However, you didn't address our recommendation/request to study the effect of proposed changes. [REDACTED] (b) (4)

[REDACTED], studies need to be performed to provide us with reasonable assurance that the alternate measure employed (revised carton and container labels) provide adequate visual differentiation for the patients. If you disagree with the nature of the request, it would be helpful to have an insight as to why. Please address this issue and explain your reasoning?

Thank you,

Rachel

*Rachel E. Hartford*  
**Regulatory Project Manager**  
**Division of Metabolism and Endocrinology Products**  
**Center for Drug Evaluation and Research**  
**Food and Drug Administration**  
[rachel.hartford@fda.hhs.gov](mailto:rachel.hartford@fda.hhs.gov)  
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**301-796-9712 (fax)**

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/s/

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Rachel E Hartford  
3/16/2009 08:47:00 PM  
CSO

## Hartford, Rachel

---

**From:** Hartford, Rachel  
**Sent:** Tuesday, February 24, 2009 4:13 PM  
**To:** 'Rima.Nassar@sanofi-aventis.com'  
**Cc:** Richard.Gural@sanofi-aventis.com; (b) (6)  
**Subject:** Apidra SoloStar

**Follow Up Flag:** Follow up  
**Flag Status:** Purple

**Attachments:** 09001469803027f8.pdf

Rima,

The supplement approval letter for Apidra SoloStar is attached.

Thank you,

Rachel



09001469803027f8  
pdf (3 MB)

*Rachel E. Hartford*  
**Regulatory Project Manager**  
**Division of Metabolism and Endocrinology Products**  
**Center for Drug Evaluation and Research**  
**Food and Drug Administration**  
[rachel.hartford@fda.hhs.gov](mailto:rachel.hartford@fda.hhs.gov)  
**301-796-0331 (phone)**  
**301-796-9712 (fax)**

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/s/

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Rachel E Hartford  
3/16/2009 08:44:57 PM  
CSO

## Hartford, Rachel

---

**From:** Hartford, Rachel  
**Sent:** Thursday, July 03, 2008 4:28 PM  
**To:** 'Rima.Nassar@sanofi-aventis.com'  
**Subject:** Apidra SoloStar NDA 21-629/S008

**Attachments:** NDA 21-629 S008.pdf

Rima,

I enjoyed meeting you at the Advisory Committee Meeting this week. A pdf version of today's action letter for Apidra SoloStar NDA 21-629/S008 is attached for your convenience. The earliest video conference date available is August 6, 2008. You will receive a meeting granted letter week after next.

Regards,

Rachel



NDA 21-629  
S008.pdf (38 KB)

*Rachel E. Hartford*

**Regulatory Project Manager**

**Division of Metabolism and Endocrinology Products**

**Center for Drug Evaluation and Research**

**Food and Drug Administration**

[rachel.hartford@fda.hhs.gov](mailto:rachel.hartford@fda.hhs.gov)

**301-796-0331 (phone)**

**301-796-9712 (fax)**

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/s/

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Rachel E Hartford  
3/16/2009 08:43:29 PM  
CSO

# REQUEST FOR CONSULTATION

TO (Office/Division): OSE

FROM (Name, Office/Division, and Phone Number of Requestor): Rachel Hartford, x60331, WO22 Rm 3397, DMEP, HFD-510

DATE  
22Sep08

IND NO.

NDA NO.  
21-629/S008

TYPE OF DOCUMENT  
sNDA

DATE OF DOCUMENT  
15Sep08

NAME OF DRUG  
Apidra

PRIORITY CONSIDERATION  
routine

CLASSIFICATION OF DRUG  
insulin

DESIRED COMPLETION DATE  
15Dec08

NAME OF FIRM: sanofi-aventis

## REASON FOR REQUEST

### I. GENERAL

- |  |  |  |
|--|--|--|
| <input type="checkbox"/> NEW PROTOCOL                    | <input type="checkbox"/> PRE-NDA MEETING         | <input type="checkbox"/> RESPONSE TO DEFICIENCY LETTER     |
| <input type="checkbox"/> PROGRESS REPORT                 | <input type="checkbox"/> END-OF-PHASE 2a MEETING | <input type="checkbox"/> FINAL PRINTED LABELING            |
| <input type="checkbox"/> NEW CORRESPONDENCE              | <input type="checkbox"/> END-OF-PHASE 2 MEETING  | <input type="checkbox"/> LABELING REVISION                 |
| <input type="checkbox"/> DRUG ADVERTISING                | <input type="checkbox"/> RESUBMISSION            | <input type="checkbox"/> ORIGINAL NEW CORRESPONDENCE       |
| <input type="checkbox"/> ADVERSE REACTION REPORT         | <input type="checkbox"/> SAFETY / EFFICACY       | <input type="checkbox"/> FORMULATIVE REVIEW                |
| <input type="checkbox"/> MANUFACTURING CHANGE / ADDITION | <input type="checkbox"/> PAPER NDA               | <input checked="" type="checkbox"/> OTHER (SPECIFY BELOW): |
| <input type="checkbox"/> MEETING PLANNED BY              | <input type="checkbox"/> CONTROL SUPPLEMENT      |  |

### II. BIOMETRICS

- |   |   |
|---|---|
| <input type="checkbox"/> PRIORITY P NDA REVIEW  | <input type="checkbox"/> CHEMISTRY REVIEW       |
| <input type="checkbox"/> END-OF-PHASE 2 MEETING | <input type="checkbox"/> PHARMACOLOGY           |
| <input type="checkbox"/> CONTROLLED STUDIES     | <input type="checkbox"/> BIOPHARMACEUTICS       |
| <input type="checkbox"/> PROTOCOL REVIEW        | <input type="checkbox"/> OTHER (SPECIFY BELOW): |
| <input type="checkbox"/> OTHER (SPECIFY BELOW): |   |

### III. BIOPHARMACEUTICS

- |  |  |
|--|--|
| <input type="checkbox"/> DISSOLUTION             | <input type="checkbox"/> DEFICIENCY LETTER RESPONSE  |
| <input type="checkbox"/> BIOAVAILABILITY STUDIES | <input type="checkbox"/> PROTOCOL - BIOPHARMACEUTICS |
| <input type="checkbox"/> PHASE 4 STUDIES         | <input type="checkbox"/> IN-VIVO WAIVER REQUEST      |

### IV. DRUG SAFETY

- |  |  |
|--|--|
| <input type="checkbox"/> PHASE 4 SURVEILLANCE/EPIDEMIOLOGY PROTOCOL                | <input type="checkbox"/> REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY |
| <input type="checkbox"/> DRUG USE, e.g., POPULATION EXPOSURE, ASSOCIATED DIAGNOSES | <input type="checkbox"/> SUMMARY OF ADVERSE EXPERIENCE                       |
| <input type="checkbox"/> CASE REPORTS OF SPECIFIC REACTIONS (List below)           | <input type="checkbox"/> POISON RISK ANALYSIS                                |
| <input type="checkbox"/> COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP         |  |

### V. SCIENTIFIC INVESTIGATIONS

- |                                   |                                      |
|-----------------------------------|--------------------------------------|
| <input type="checkbox"/> CLINICAL | <input type="checkbox"/> NONCLINICAL |
|-----------------------------------|--------------------------------------|

COMMENTS / SPECIAL INSTRUCTIONS: PDUFA goal date is 15Jan08. This is sanofi's complete response which contains the color differentiation study results. Please review the carton label, container label, and color differentiation study results. The network location is : \\FDSWA150\NONECTD\N21629\S\_008\2008-09-15

SIGNATURE OF REQUESTOR  
Rachel Hartford

METHOD OF DELIVERY (Check one)  
 DFS       EMAIL       MAIL       HAND

PRINTED NAME AND SIGNATURE OF RECEIVER

PRINTED NAME AND SIGNATURE OF DELIVERER

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/s/

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Rachel E Hartford  
9/22/2008 02:16:56 PM



NDA 21-629/S-008

sanofi aventis U.S. LLC  
Attention: Rima Nassar, Ph.D.  
Regulatory Development  
200 Crossing Boulevard, Mailstop: BX4-206A  
Bridgewater, NJ 08807

Dear Dr. Nassar:

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

We also refer to your June 30, 2008, meeting request to discuss our comments on your color differentiation study. Your July 31, 2008, email requesting cancellation of our August 6, 2008, meeting stated that the answers and comments in the preliminary meeting minutes sent via email on July 30, 2008 were satisfactory.

A copy of our internal meeting minutes is attached for your information; the minutes are the same as the July 30, 2008, version.

If you have any questions, call me at 301-796-0331.

Sincerely,

*{See appended electronic signature page}*

Rachel Hartford  
Regulatory Project Manager  
Division of Metabolism and Endocrinology Products  
Office of Drug Evaluation II  
Center for Drug Evaluation and Research

## QUESTIONS

Your questions are repeated below, followed by our responses in bold.

Question 1: The comments sent by the Agency state that the study should include a poorly differentiated pair of Apidra SoloStar and Lantus SoloStar in parallel with the proposed Apidra SoloStar and currently marketed Lantus SoloStar pens. It is not clear to the sponsor why these poorly differentiated pens should be included in the study or how to design/assemble these pens. Can the Agency provide the sponsor with direction and guidance on the need to include the poorly differentiated pens in the study and on the design/assembly required for these pens?

**FDA Response: The rationale for using a poorly differentiated pair of pens is to provide a baseline rate of selection error. We believe establishing a baseline rate of selection error for two pens that lack differentiation will give context for interpreting the selection errors observed in the parallel study of the proposed Apidra SoloStar pen device.**

**The design of the “Poorly” differentiated SoloStar pens presented in the July 10, 2008, submission is adequate. The Agency has no further guidance to offer on the design/assembly for these pens.**

Question 2: The sponsor has several questions related to the general methodology of the study such as the recommended monadic design and would like to discuss these with the Agency prior to the initiation of the study. Can the Agency provide further clarification to the monadic design recommended for the study?

**FDA Response: The intent of the monadic design (Question 12 of the proposed protocol) is to assess the patient’s ability to correctly identify the SoloStar pens in isolation from one another. We recommend that this aspect be assessed because confirmation bias plays a role in product selection errors. Confirmation bias contributes to medication errors because when selecting products, humans tend to perceive confirming evidence (e.g., color, shapes, font type, symbols, etc.) more readily than disconfirming evidence (e.g., differences in product nomenclature). We note that there are underlying similarities in the proposed Apidra SoloStar pen and the Lantus SoloStar relating to color (blue vs. grey), packaging (pen), symbols (stripe bars), labels (b) (4) which may predispose consumers to confirmation bias and selection errors. Moreover, root cause analysis of medication errors involving currently marketed Apidra and Lantus products (vials, cartridges) suggests that the similar packaging and labeling of the products creates confirmation bias that is contributing to consumer and practitioner selection errors in some cases. Thus, we believe that it is important to assess if subjects can discriminate the two pens from one another in isolation as well as when presented next to each other.**

Question 3: The sponsor would like to discuss the recruiting criteria prior to initiation of the study, as the subject selection may have an impact on the study outcome. Can the Agency provide further clarification on the recruiting criteria for subjects included in the study?

**FDA Response: Recruit approximately 200 individuals with diabetes representative of the potential Apidra SoloStar users. Age, ethnicity, education, literacy, gender, and employment status of the study subjects should be similar to the current users of the Apidra vial or cartridges.** [REDACTED] (b) (4)

[REDACTED] some patients should be maintained on oral medication therapy only, and others should be insulin users. The screening questions in the proposed study appear appropriate.

**Additional Comment: We have reviewed your proposed Pen Color Differentiation Study submitted on July 10, 2008. The study follows the advice in our June 27, 2008, correspondence.**

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/s/

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Rachel E Hartford  
8/14/2008 11:34:48 AM



NDA 21-629/S-008

sanofi aventis U.S., Inc.  
Attention: Rima Nassar, Ph.D.  
Regulatory Development  
200 Crossing Boulevard, Mailstop: BX4-206A  
Bridgewater, NJ 08807

Dear Dr. Nassar:

Please refer to your supplemental new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Apidra (insulin glulisine [rDNA human insulin analog]) injection

We also refer to the June 11, 2008, meeting to discuss the carton and container labels for S- 008.

(b) (4)

We have reviewed the referenced material and have the following comments and recommendations.

The safety concern is that the proposed Apidra SoloStar pen is not adequately differentiated from the Lantus SoloStar pen which may lead to medication errors in which the wrong drug is administered. These safety concerns arose during review of the supplemental applications for these products which noted the overall similarity of the pen design, similar color schemes of the pen body (blue versus grey), the similarity of the nomenclature (Apidra **SoloStar** versus Lantus **SoloStar**; **insulin glulisine** versus **insulin glargine**), and the similarity introduced by similar label design (layout, typography, candy-stripe bar graphics, etc.).

These safety concerns are augmented by our review of medication errors involving currently marketed Apidra and Lantus products. Root cause analysis consistently indicates that similar packaging and label design contribute to the ongoing medication errors with Apidra and Lantus products. Many of the medication errors involved the administration of the wrong drug and are associated with serious adverse events.

Given these safety concerns and the ongoing Apidra and Lantus medication errors, we request that you study the proposed Apidra SoloStar pen device and labeling to assess if patients with diabetes are able to reliably discriminate the proposed Apidra pen from the currently marketed Lantus SoloStar pen. We also request that you study the ability of patients to correctly identify the Apidra SoloStar Pen in isolation, since the similar pen features may predispose patients to confirmation bias when viewing the pens in isolation.

Suggested study specifics:

**Objectives:**

Primary objectives of the study might include:

- To measure the error rate of patients when selecting and identifying the Apidra SoloStar pen
- To measure the degree of error rate difference between a poorly differentiated packaging alternative compared with the proposed Apidra SoloStar pen and currently marketed Lantus SoloStar pen among patients with diabetes.

Secondary objectives of the study might include:

- To collect qualitative data to understand which features patients use to select the pen device.

**Methods:**

A poorly differentiated pair of Apidra SoloStar and Lantus SoloStar pens should be studied in parallel with the proposed Apidra SoloStar and currently marketed Lantus SoloStar Pens.

Subjects should be divided into two groups (I, II).

A poorly differentiated pair of pens might be best represented by employing two SoloStar pens that are identical in every feature (design, color, labels,etc) EXCEPT name.

The rationale for using a poorly differentiated pair of pens is to provide a baseline error rate. We believe this will help to give context to the selection rate errors observed in the parallel study of the proposed Apidra SoloStar pen device.

**Measures**

The primary outcome measure for this study protocol is error percentage rate. An error can be defined as the incorrect selection/identification or inability to select/identify the correct SoloStar pen in each of the case scenarios presented in the questionnaire. The rate is based on the overall number of observations (three scenarios per subject).

**Subjects:**

Recruit approximately 200 individuals with diabetes representative of the potential Apidra SoloStar users. Age, ethnicity, education, literacy, gender, and employment status of the study subjects should be similar to the current users of the Apidra vial or cartridges. (b) (4)

[REDACTED]

(b) (4) some patients should be maintained on oral medication therapy only, and others should be insulin users. Screening questions S6, S7, S8, S9 are appropriate for capturing the relevant information.

### **Screening Questionnaire:**

We do not believe Question S4 should be used to screen subjects. It should be retained to collect relevant information about the subject's vision, and believe that subjects who do not have their glasses or contact lenses with them should be included in the study. Individuals with uncorrected vision may administer Apidra SoloStar under real-use conditions.

### **Main Questionnaire**

The text, scenarios, and questions should all be read by the interviewer orally to the respondent, not given to the respondent in writing to read.

(b) (4)

The questionnaire should be revised to a case-based format to more adequately assess the patient's ability to discriminate the pens. The purpose of the study is to see *how* or *if* a person can differentiate between the two pens. Therefore, you should not use the name of the products in the questionnaire. By using product names, you are providing study participants with one mechanism that can be used to differentiate the products. Instead, the goal should be to allow the study participants to self-identify differentiating features of the pens (e.g., name, color, label, etc.) without input from the study personnel.

Language which may be appropriate is as follows:

“We are testing the appearance of two pens that diabetes patients might use to take insulin and we are very interested in your feedback.”

“This insulin [show Lantus SoloStar] is used one time each day. “

“This insulin [show Apidra SoloStar] is used three times a day with your meals.”

- **ASK RESPONDENT TO REVIEW ALL ASPECTS OF THE PENS AND THEN PLACE THE PENS BACK ON THE TABLE.**
- **THE INTERVIEWER SHOULD MIX UP THE PENS SO THAT THE RESPONDENT ISN'T ABLE TO ASSOCIATE THE POSITION OF THE PENS WITH THE IDENTITY OF THE PENS.**

“I am now going to ask you to tell me which pen you would use based on the information in the scenarios:”

Q1. “You are about to eat lunch. You need to give yourself the insulin that is used three times a day. Please pick up the pen that you need to use.”

- 1 Yes, correctly selected the pen
- 2 No, incorrectly selected the pen
- 3 Doesn't know **TERMINATE**

Q2. “ It is 9 o'clock at night and you are getting ready for bed. You need to give yourself the insulin that is used one time a day. Please pick up the pen that you need to use. “

- 1 Yes, correctly selected the pen
- 2 No, incorrectly selected the pen
- 3 Doesn't know **TERMINATE**

Q3. “You are getting your breakfast ready, and need to give yourself your insulin that is used three times a day. Please select the appropriate pen.”

- 1 Yes, correctly selected the pen
- 2 No, incorrectly selected the pen
- 3 Doesn't know **TERMINATE**

For each incorrect or correct response, the interviewer should ask questions to identify the features that patients use to select the pen. An appropriate question might be:

“When you look at the pen you selected, could you tell me why you picked this pen?”

If the patient doesn't know what pen to select, an appropriate follow-up question might be:

“You seem unsure of which pen you should use. Can you tell me why you are not sure?”

[REDACTED] (b) (4)

[REDACTED] (b) (4)

[REDACTED] (b) (4)

[REDACTED] (b) (4)

**Q.1c (p 16):** Retain with no modification.

**INTERVIEWER: TAKE PENS BACK FROM RESPONDENT AND STORE THEM OUT OF SIGHT.**

Inform the patient that you have just a few more questions for classification purposes only. We suggest retaining classification questions Q.4, Q.5., Q.6, Q.7, Q.8, Q.9, without modification.

*To assess the patient's ability to correctly identify the SoloStar pens in isolation from one another, add an additional scenario after concluding the classification questions.*

Inform the patient that you have just one more question for them to answer. Retain all pens out of sight.

For this scenario, each of the parallel groups (I, II) should be evenly divided into two groups (A, B).

**Groups IA, IIA: INTERVIEWER RETRIEVE AND GIVE TO THE SUBJECT AN APIDRA SOLOSTAR PEN. VERBALLY ASK:**

“It is time to give yourself your one time a day insulin. Is this the right insulin pen?”

- Yes
- No
- Not sure

“How did you know that this was/was not the right pen?”

**Groups IB, IIB: INTERVIEWER RETRIEVE AND GIVE TO THE SUBJECT AN APIDRA SOLOSTAR PEN. VERBALLY ASK:**

“You are about to eat a dinner. It is time to give yourself your three times a day insulin. Is this the right insulin pen?”

- Yes
- No
- Not sure

“How did you know that this was/was not the right pen?”

If you have any questions, call Rachel Hartford, Regulatory Project Manager, at 301-796-0331.

Sincerely,

*{See appended electronic signature page}*

Mary H. Parks, M.D.  
Director  
Division of Metabolism and Endocrinology Products  
Office of Drug Evaluation II  
Center for Drug Evaluation and Research

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/s/

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Mary Parks  
6/27/2008 09:31:49 AM

## REQUEST FOR CONSULTATION

TO (Office/Division): OSE

FROM (Name, Office/Division, and Phone Number of Requestor): Rachel Hartford, x60331, WO22 Rm 3397, DMEP, HFD-510

DATE  
10Mar08

IND NO.

NDA NO.  
21-629/S008

TYPE OF DOCUMENT  
Complete Response

DATE OF DOCUMENT  
3Mar08

NAME OF DRUG  
Apidra

PRIORITY CONSIDERATION

CLASSIFICATION OF DRUG  
insulin

DESIRED COMPLETION DATE  
19Jun2008

NAME OF FIRM: sanofi-aventis

### REASON FOR REQUEST

#### I. GENERAL

- |  |  |   |
|--|--|---|
| <input type="checkbox"/> NEW PROTOCOL                    | <input type="checkbox"/> PRE-NDA MEETING         | <input checked="" type="checkbox"/> RESPONSE TO DEFICIENCY LETTER |
| <input type="checkbox"/> PROGRESS REPORT                 | <input type="checkbox"/> END-OF-PHASE 2a MEETING | <input type="checkbox"/> FINAL PRINTED LABELING                   |
| <input type="checkbox"/> NEW CORRESPONDENCE              | <input type="checkbox"/> END-OF-PHASE 2 MEETING  | <input type="checkbox"/> LABELING REVISION                        |
| <input type="checkbox"/> DRUG ADVERTISING                | <input checked="" type="checkbox"/> RESUBMISSION | <input type="checkbox"/> ORIGINAL NEW CORRESPONDENCE              |
| <input type="checkbox"/> ADVERSE REACTION REPORT         | <input type="checkbox"/> SAFETY / EFFICACY       | <input type="checkbox"/> FORMULATIVE REVIEW                       |
| <input type="checkbox"/> MANUFACTURING CHANGE / ADDITION | <input type="checkbox"/> PAPER NDA               | <input type="checkbox"/> OTHER (SPECIFY BELOW):                   |
| <input type="checkbox"/> MEETING PLANNED BY              | <input type="checkbox"/> CONTROL SUPPLEMENT      |   |

#### II. BIOMETRICS

- |   |   |
|---|---|
| <input type="checkbox"/> PRIORITY P NDA REVIEW  | <input type="checkbox"/> CHEMISTRY REVIEW       |
| <input type="checkbox"/> END-OF-PHASE 2 MEETING | <input type="checkbox"/> PHARMACOLOGY           |
| <input type="checkbox"/> CONTROLLED STUDIES     | <input type="checkbox"/> BIOPHARMACEUTICS       |
| <input type="checkbox"/> PROTOCOL REVIEW        | <input type="checkbox"/> OTHER (SPECIFY BELOW): |
| <input type="checkbox"/> OTHER (SPECIFY BELOW): |   |

#### III. BIOPHARMACEUTICS

- |   |  |
|---|--|
| <input type="checkbox"/> DISSOLUTION            | <input type="checkbox"/> DEFICIENCY LETTER RESPONSE  |
| <input type="checkbox"/> BIOAVAILABILTY STUDIES | <input type="checkbox"/> PROTOCOL - BIOPHARMACEUTICS |
| <input type="checkbox"/> PHASE 4 STUDIES        | <input type="checkbox"/> IN-VIVO WAIVER REQUEST      |

#### IV. DRUG SAFETY

- |  |  |
|--|--|
| <input type="checkbox"/> PHASE 4 SURVEILLANCE/EPIDEMIOLOGY PROTOCOL                | <input type="checkbox"/> REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY |
| <input type="checkbox"/> DRUG USE, e.g., POPULATION EXPOSURE, ASSOCIATED DIAGNOSES | <input type="checkbox"/> SUMMARY OF ADVERSE EXPERIENCE                       |
| <input type="checkbox"/> CASE REPORTS OF SPECIFIC REACTIONS (List below)           | <input type="checkbox"/> POISON RISK ANALYSIS                                |
| <input type="checkbox"/> COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP         |  |

#### V. SCIENTIFIC INVESTIGATIONS

- |                                   |                                      |
|-----------------------------------|--------------------------------------|
| <input type="checkbox"/> CLINICAL | <input type="checkbox"/> NONCLINICAL |
|-----------------------------------|--------------------------------------|

**COMMENTS / SPECIAL INSTRUCTIONS:** Please indicate if this is or isn't a complete response by 17Mar08.

Please review sanofi-aventis' complete response to our 18Jan08 approvable letter citing deficiencies in the instruction leaflet, pen and carton labels, pen name, and color scheme.

The network location is : \\CDSESUB1\NONECTD\N21629\S\_008\2008-03-03

SIGNATURE OF REQUESTOR  
Rachel Hartford

METHOD OF DELIVERY (Check one)  
 DFS       EMAIL       MAIL       HAND

PRINTED NAME AND SIGNATURE OF RECEIVER

PRINTED NAME AND SIGNATURE OF DELIVERER

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/s/

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Rachel E Hartford  
3/10/2008 05:02:36 PM

DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION		<b>REQUEST FOR CONSULTATION</b>		
TO (Office/Division): OSE: 1-DDRE, 2-DMETS, 3-DSCRS		FROM (Name, Office/Division, and Phone Number of Requestor): Rachel Hartford, 60331, WO22 Rm3397, DMEP, HFD-510		
DATE 14Nov2007	IND NO.	NDA NO. 21-629/S008	TYPE OF DOCUMENT Packaging Supplement	DATE OF DOCUMENT 14Sep2007
NAME OF DRUG Apidra	PRIORITY CONSIDERATION		CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE 4Jan2008
NAME OF FIRM: sanofi aventis				
<b>REASON FOR REQUEST</b>				
<b>I. GENERAL</b>				
<input type="checkbox"/> NEW PROTOCOL	<input type="checkbox"/> PRE-NDA MEETING	<input type="checkbox"/> RESPONSE TO DEFICIENCY LETTER		
<input type="checkbox"/> PROGRESS REPORT	<input type="checkbox"/> END-OF-PHASE 2a MEETING	<input type="checkbox"/> FINAL PRINTED LABELING		
<input type="checkbox"/> NEW CORRESPONDENCE	<input type="checkbox"/> END-OF-PHASE 2 MEETING	<input type="checkbox"/> LABELING REVISION		
<input type="checkbox"/> DRUG ADVERTISING	<input checked="" type="checkbox"/> RESUBMISSION	<input type="checkbox"/> ORIGINAL NEW CORRESPONDENCE		
<input type="checkbox"/> ADVERSE REACTION REPORT	<input type="checkbox"/> SAFETY / EFFICACY	<input type="checkbox"/> FORMULATIVE REVIEW		
<input type="checkbox"/> MANUFACTURING CHANGE / ADDITION	<input type="checkbox"/> PAPER NDA	<input type="checkbox"/> OTHER (SPECIFY BELOW):		
<input type="checkbox"/> MEETING PLANNED BY	<input type="checkbox"/> CONTROL SUPPLEMENT			
<b>II. BIOMETRICS</b>				
<input type="checkbox"/> PRIORITY P NDA REVIEW	<input type="checkbox"/> END-OF-PHASE 2 MEETING	<input type="checkbox"/> CHEMISTRY REVIEW		
<input type="checkbox"/> CONTROLLED STUDIES	<input type="checkbox"/> PROTOCOL REVIEW	<input type="checkbox"/> PHARMACOLOGY		
<input type="checkbox"/> OTHER (SPECIFY BELOW):		<input type="checkbox"/> BIOPHARMACEUTICS		
		<input type="checkbox"/> OTHER (SPECIFY BELOW):		
<b>III. BIOPHARMACEUTICS</b>				
<input type="checkbox"/> DISSOLUTION	<input type="checkbox"/> BIOAVAILABILTY STUDIES	<input type="checkbox"/> DEFICIENCY LETTER RESPONSE		
<input type="checkbox"/> PHASE 4 STUDIES		<input type="checkbox"/> PROTOCOL - BIOPHARMACEUTICS		
		<input type="checkbox"/> IN-VIVO WAIVER REQUEST		
<b>IV. DRUG SAFETY</b>				
<input type="checkbox"/> PHASE 4 SURVEILLANCE/EPIDEMIOLOGY PROTOCOL	<input type="checkbox"/> DRUG USE, e.g., POPULATION EXPOSURE, ASSOCIATED DIAGNOSES	<input type="checkbox"/> REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY		
<input type="checkbox"/> CASE REPORTS OF SPECIFIC REACTIONS (List below)	<input type="checkbox"/> COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP	<input type="checkbox"/> SUMMARY OF ADVERSE EXPERIENCE		
		<input type="checkbox"/> POISON RISK ANALYSIS		
<b>V. SCIENTIFIC INVESTIGATIONS</b>				
<input type="checkbox"/> CLINICAL		<input type="checkbox"/> NONCLINICAL		
<b>COMMENTS / SPECIAL INSTRUCTIONS:</b> The submission is in the edr and can also be accessed via the link: \\CDSESUB1\N21629\S_008\2007-09-14. Sample Lantus and Apidra Solo Star Pens were provided by sanofi-aventis for the reviewers; please return to DMEP upon review completion. 1-DDRE: Please provide comments or suggestions for labeling based on any adverse event reports for the Lantus Solo Star pen. 2-DMETS: Please review the carton label, container label, and any other piece(s) of labeling appropriate for the Apidra Solo Star pen. 3-DSCRS: Review the instruction leaflet and PPI for the Apidra Solo Star Pen.				
SIGNATURE OF REQUESTOR Rachel E. Hartford		METHOD OF DELIVERY (Check one) <input checked="" type="checkbox"/> DFS <input type="checkbox"/> EMAIL <input type="checkbox"/> MAIL <input type="checkbox"/> HAND		
PRINTED NAME AND SIGNATURE OF RECEIVER		PRINTED NAME AND SIGNATURE OF DELIVERER		

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this page is the manifestation of the electronic signature.**  
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/s/

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Rachel E Hartford  
11/14/2007 06:37:47 PM

**Galliers, Enid M**

**From:** Watson, Anthony [anthony.watson@fda.hhs.gov]  
**Sent:** Friday, February 23, 2007 3:12 PM  
**To:** Galliers, Enid M  
**Subject:** FW: NDA 21-081 S024

**Attachments:** NDA 21-081 S024 Lantus SoloStar Rv1 Final.doc

Anthony D. Watson, BS, MS, MBA  
Chief, General Hospital Devices Branch  
Division of Anesthesiology, General Hospital, Infection Control, and Dental  
Devices  
Center for Devices and Radiological Health  
U.S. Food and Drug Administration  
Tel: (240) 276-3707  
Fax: (240) 276-3789

---

**From:** Soprey, Pandu  
**Sent:** Monday, February 05, 2007 11:11 AM  
**To:** Galliers, Enid M  
**Cc:** Watson, Anthony; OC Combination Products  
**Subject:** NDA 21-081 S024



NDA 21-081  
4 Lantus SoloSt

Attached is Consult Review Memo

Pandu R Soprey Ph D  
Microbiologist  
FDA/ODE/DAGID/GHDB  
Tel: 240-276-3707 Fax 240-276-3789  
[Pandu.Soprey@fda.hhs.gov](mailto:Pandu.Soprey@fda.hhs.gov)

## **COSULT REVIEW MEMO**

**DATE:** February 2, 2007

**TO:** Enid M. Galliers CDER/DMEP/HFD-510

**FROM:** Pandu R. Soprey, Ph.D.  
Review Scientist, CDRH/ODE/DAGID HFZ-480

**THROUGH:** Anthony Watson Branch Chief GHDB/DAGID/CDRH/ HFZ-480

**SUBMISSION:** NDA 21-081/S-024 Lantus (insulin glargine [rDNA origin]) Injection  
NDA 21-629/S-008 Apidra (insulin glulisine [rDNA origin]) Injection

### **DEVICE:**

Proprietary Name: SoloStar disposable Pen Injector for Lantus insulin and SoloStar disposable Pen Injector for Apidra insulin

Non-proprietary: Pen injector, Syringe containing insulin in a 3mL disposable cartridge

### **APPLICANT / SPONSOR:**

Sanofi-Aventis

### **INTENT/PURPOSE OF THIS SUBMISSION:**

The applicant has provided responses to the deficiencies listed in the approvable letter (dated August 24, 2006) for Lantus SoloStar and Apidra SoloStar. The responses to the deficiencies are provided in Supplement #24 dated October 24, 2006 and December 14, 2006

### **REVIEW OF DEVICE RELATED RESPONSES:**

#### **Response #2**

In its initial position, tactile features on the dosage selector and the pen body are aligned “0” is displayed in the dose window and the dial will be at zero. The dose to be injected is then pre-selected by rotating a dosage selector at the rear end of the device and then the number of selected insulin units is displayed in the dose window on the side of the pen. After an injection of the selected dose the injection button reverts back to the original position and “0” is displayed in the dose window. Display of “0” assures that the dose delivery is complete.

The response explains how the dose delivery is complete, the response is acceptable.

#### **Response #3**

Dialing beyond the maximum dose of 80 units is not possible. If the patient tries to select a higher dose, the number sleeve and dose window engage rotationally preventing the number sleeve from moving further. The dosage selector and number sleeve are firmly affixed to each other during the assembly process.

All physical dose-setting limits (maximum dose, minimum dose, end of cartridge) have been tested and demonstrate a mechanical strength that will withstand forces typically applied by patients. Furthermore, torque required to set the dose was evaluated as well as the correlation between visual and audible feedback (i.e. the number of clicks correspond to units displayed in dose window).

Since SoloStar is a mechanically operated device, rapid dialing has no effect on accuracy of dose setting or injection. The number sleeve of the pen has two functions; it indicates the number of insulin units to be injected

and simultaneously sets the dose in the pen. Thus, dose indication and dose setting are physically linked and rapid dialing has no impact on the accuracy of the insulin pen.

The device was evaluated according to ISO Standard (ISO 11608:2000, Pen-injectors for medical use, Part 1: Requirements and test methods) test requirements. The device set at three different doses (1-unit, 40 units and 80 units) were tested at standard atmosphere (ISO 11608-1 Section 6.1), cool atmosphere (ISO 11608-1 Section 6.2), hot atmosphere (ISO 11608-1 Section 6.3), after preconditioning (ISO 11608-1 Section 7.1 and 7.2) and free fall testing (ISO 11608-1 Section 7.4b). The various tests results met the specification limits for all of the three dose volumes (1 U, 40 U and 80 U). The columns "calculated lower end of distribution (LED)" and "calculated upper end of distribution (UED)" are calculated from the confidence interval.

The response provided in the supplement shows that the device meets the dose selection and dose delivery requirements. The response is acceptable.

**Response #4**

The accuracy of the last dose was determined and found to be in compliance with the standard (ISO11608-1). Testing is performed in accordance with the ISO 11608-2 instructions. The test is conducted by placing a cartridge in an apparatus described in the ISO norm (ISO 11608-2). The liquid expelled from the cartridge is collected, and the volume delivered after the plunger displacement is then measured. All dose accuracy calculations are carried out in units of milliliters.

The initial position of the rubber stopper related to the shoulder of the glass cartridge defines how many units can be accurately delivered in total, i.e. the length of the cylindrical part of the cartridge. The mechanism was designed to ensure the rubber stopper cannot be pushed further than the cylindrical part of the glass cartridge during dosing. This is accomplished through the presence of a physical part which prevents additional advance of the mechanism beyond the last dose. Therefore the patient can dial only up to the dose left in the cartridge.

The response provided satisfies the dose delivery requirements. The response is acceptable.

**Response #5:**

Lantus® SoloStar® is not an auto injector and does not contain any external source of energy to deliver an insulin dose and the dose must be delivered manually by constant pressure from the patient on the activator. The dose is delivered manually by pressing the button inward until it is in its starting position and the dose window displays "0". Thus accidental firing is not possible. In addition, the patient leaflet mentioned that the needle needs to be removed after each injection by the patient. Without a needle the cartridge is sealed and no accidental firing is possible

The response is acceptable.

**Response #6:**

The applicant has identified the needles to be used with SoloStar pen injector. For Lantus SoloStar, the needles to be used with SoloStar injector are BD Ultra-Fine needles. This sentence will also be included in the Lantus "Instructions for SoloStar use": (b) (4)

The response is acceptable.

**Response #7:**

The sponsor has clarified function of the injection button and provided rationale for end position of the injection delivery button. When the injector button is in its initial position, tactile features on the dosage selector and the pen body are aligned, "0" is displayed in the dose window. The dose to be injected is pre-selected by rotating the

dosage selector at the rear end of the device. The number of selected insulin units is displayed in the dose window on the side of the pen. The dose is delivered by pressing the button until it is in its original position, in which “0” is displayed in the dose window. Mechanical constraints prevent the user from pushing the button any further beyond zero. Finally, the patient instruction manual instructs the patient to delay removal of the SoloStar for 10 seconds after the injection button is in the original position (when the injection button is in the original position and 0 is displayed in the dose window) to assure dose delivery is complete.

The response is acceptable.

**Response #8:**

This risk management process study is performed according to (b) (4) and applicable internal SOPs. In this process human factors and device specific factors as well as misuse or abuse scenarios are investigated, evaluated, corresponding mitigations if necessary were planned and implemented. The successful implementations of these factors were verified.

Usability studies are conducted to predict the potential for human error and misuse/abuse to occur. Final user testing is performed in a design validation study before market release of the device and after launch a post-market surveillance system is in place. Complaints and adverse events are continuously monitored, trended, investigated when necessary and used to update the risk management. Findings out of the Risk Management Process are used to improve the product if necessary and provide valuable contributions for the development of new devices.

The detailed information related to the performance and safety of the device is provided under the following description:

**Intended Use:**

The detailed description of intended use of SoloStar pen injector under different use different conditions are listed and described.

**Functional Analysis:**

Analysis of SoloStar was prepared which described logical representation of the relations of the input and output functions and this information was used as basis for a systematic review of all hazards related to each identifiable output function of the device.

(b) (4)



(b) (4)

**RISK MANAGEMENT:**

The definition of the acceptable risk level was based on the standard (b) (4), risk analysis for medical devices. In order to estimate the risks and to establish acceptable risk levels for SoloStar, a Risk Chart (Pg. 12) was used as qualitative categorization method. Using this chart the estimation of the risk of harm is divided into the probability of its occurrence and its severity. Seven severity classes were identified (fatal, life threatening, serious, non-serious, negligible, customer complaint, and customer reassurance. Performing a risk assessment the probability of occurrence of harm was estimated for all defined hazards associated with the output functions identified in the functional analysis.

The risk assessment was performed by an expert team consisting of representatives of various functions in the company. Additionally ergonomic specialists from an external company created abuse/misuse scenario and human factors assessments for SoloStar. These studies were taken into consideration while preparing the risk assessment. The results of the risk assessment for SoloStar before and after mitigation (risk control) were considered and summarized in the figures (Pg. 14).

Individual risks (128 risks) were evaluated and the occurrence of the adverse effect of basal (Lantus insulin) and short acting insulin (Apidra) were evaluated separately. After mitigation, for both the majority was found in the Generally Acceptable category, none of the risks are in the Not Acceptable category. 30 cases for both basal and short acting insulin remained in the region (“ALARP”). This represents a risk to patients with an extremely low probability of occurrence.

**RISK - BENEFIT ANALYSIS:**

The results of the risk assessment show that the use of SoloStar with insulin, like Lantus®, is associated with some risks that require risk control measures. A number of mitigations are already in place and effectiveness was verified.

The better part of the remaining overall residual risk can be associated with the proper use of the pen, with needle handling, with the potential risk to apply the wrong insulin or to use training pens filled with water (mix-up) and with needle pricking.

As per plan complaints and adverse events will be continuously monitored, trended and investigated (when required) after launch during post-market surveillance and used to update the risk management. The overall residual risk of SoloStar® was discussed and agreed in a cross-functional team meeting together with the Risk Management Board. All individual risks falling into the ALARP (As Low As Reasonably Practicable) region were presented to the Risk Management Board. Mitigations were discussed and agreed.

It was concluded that the intended benefit for the patients associated with the use of the SoloStar with insulin, like Lantus, outweighs the remaining overall residual risk

**DESIGN VALIDATION STUDY**

SoloStar pen injector was tested in a design validation study and the primary objective was to validate the use of the pen device by the target patient population (patients diagnosed with type 1 or type 2 diabetes mellitus) under two different scenarios, with or without face-to-face training by a healthcare professional:

Scenario #1 (Phase 1): This scenario was designed to simulate a clinical practice environment where active face-to-face training by the healthcare professional would take place, prior to the subjects receiving the pen injector.  
Scenario #2 (Phase 2): This scenario was designed to simulate a clinical practice environment where the subject

would receive the pen and instructional leaflet, without any training by a healthcare professional. The subject would then self-train on how to use the pen with the instructions provided, and if necessary, request additional training via the sanofi-aventis (S-A) Help Line Call Center, or by contacting the healthcare professional by telephone. After training or self training, subjects were asked to show how to correctly deliver a dose, three times, each time with 3 different pens.

The study objective was assessed for each phase separately by the following endpoints: a) Primary endpoint: The proportion of subjects who delivered a successful dose on all three-dose delivery repetitions. b) Secondary endpoints: The proportion of subjects who performed the safety test (pre-dose actuation) correctly before each of the three dose delivery repetitions, the proportion of dose delivery repetitions with correctly performed safety tests, the proportion of repetitions for which a successful dose was delivered, the proportion of subjects who used the S-A Help Line Call Center or requested additional instructions (in person [Phase 1 only] or by telephone) from a healthcare professional after the initial training session, the proportion of subjects who made use of the instructional leaflet after the initial training session, and the accuracy and precision of the device based on the three dose injections (weights) per subject. Safety variables included the following: The incidence of adverse events (AEs) by primary term and Product Technical Complaints (PTCs).

The study population consisted of a total of 181 subjects (86 in Phase 1; 95 in Phase 2) and the safety population consisted of a total of 204 subjects (100 in Phase 1; and 104 in Phase 2). There were 50 validation subjects Phase 1 and 54 in Phase 2.

The results of the Efficacy and Safety study showed that the primary and secondary study criteria were met and the conclusions of the design validation study were:

- i) The use of the SoloStar pen device was successfully validated by subjects with type 1 and 2 diabetes mellitus (the target population) in both the Phase 1 and Phase 2 scenarios, with and without face-to-face training, respectively.
- ii) Subjects using the SoloStar pen device accurately delivered the dose that was dialed.
- iii) In Phase 1, the subjects delivered dose was confirmed to be accurate and the variability of the delivered dose was low. Although in Phase 2, accuracy could not be confirmed based on the SAP pre-defined interval when the outliers were excluded the delivered dose was observed to be accurate with a reduction in the among subject variability.
- iv) The effect of safety test performance on the delivered dose was deemed not to be clinically relevant.
- v) There were no adverse events or pen malfunctions. One PTC was reported however was determined to be due to a bent needle and not the pen device.

The response is acceptable.

**COMMENTS AND CONCLUSION:**

The applicant has provided adequate responses to the device related deficiencies (deficiencies #2 through #8). From a device viewpoint the pen-injector described in NDA 21-32 S024 may be approved.

Pandu R. Soprey  
Scientific Reviewer, CDRH, HFZ-480

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/s/

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Enid Galliers

2/23/2007 03:44:34 PM

CSO

Checking CDRH review into DFS on behalf of Pandu  
Soprey & Anthony Watson.

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/s/

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Rachel E Hartford  
9/21/2007 06:30:42 PM  
CSO  
Entering this review on behafl CDRH

**For Consulting Center Use Only:**

Date Received: \_\_\_\_\_

Assigned to: \_\_\_\_\_

Date Assigned: \_\_\_\_\_

Assigned by: \_\_\_\_\_

Completed date: \_\_\_\_\_

Reviewer Initials: \_\_\_\_\_

Supervisory Concurrence: \_\_\_\_\_

## Intercenter Request for Consultative or Collaborative Review Form

**To (Consulting Center):**

Center:

Division: ODE/DAGID/GHDB

Mail Code: HFZ-480

Consulting Reviewer Name: Anthony Watson

Building/Room #: Corporate Bldg, RM340D

Phone #: 301-594-1287 x169

Fax #:

Email Address: anthony.watson@hhs.cdrh.gov

RPM/CSO Name and Mail Code:

**From (Originating Center):**

Center: CDER

Division: DMEP

Mail Code: HFD-510

Requesting Reviewer Name: Janice Brown

Building/Room #: WO Bldg 21, RM 2662

Phone #: 301-796-1652

Fax #:

Email Address: janice.brown@hhs.cder.gov

RPM/CSO Name and Mail Code: Julie Rhee, DMEP

Requesting Reviewer's Concurring

Supervisor's Name: James Vidra, Ph.D.

**Receiving Division: If you have received this request in error, you must contact the request originator by phone immediately to alert the request originator to the error.**

Date of Request: May 15, 2006

**Requested Completion Date:** August 15, 2006

Submission/Application Number: NDA 21-629/S-008  
(Not Barcode Number)

Submission Type: NDA  
(510(k), PMA, NDA, BLA, IND, IDE, etc.)

Type of Product:  Drug-device combination     Drug-biologic combination     Device-biologic combination  
 Drug-device-biologic combination     Not a combination product

Submission Receipt Date: April 24, 2006

Official Submission Due Date: August 24, 2006

Name of Product:

Name of Firm:

Intended Use:

Brief Description of Documents Being Provided (e.g., clinical data -- include submission dates if appropriate):

Documents to be returned to Requesting Reviewer?     Yes     No

**Complete description of the request.** Include history and specific issues, (e.g., risks, concerns), if any, and specific question(s) to be answered by the consulted reviewer. The consulted reviewer should contact the request originator if questions/concerns are not clear. Attach extra sheet(s) if necessary:

Type of Request:     Consultative Review     Collaborative Review

(940 characters max -- use additional sheet if necessary)

Please review dose accuracy and precision of Lantus SoloStar pen. In addition, please review all information in section 3.2.P.7 Container Closure System which includes device components, specifications, methods, and assembly process description.

The sponsor also submitted a supplement for SoloStar pen to NDA 21-081 for Lantus (S-024). I'll request a separate consult for Lantus.

This supplement is submitted electronically; however, a hard copy of the section 3.2.P.7 is included with this request. If you need any additional information, please call Julie Rhee at 301-796-1280. Thank you.

## Rhee, H Julie

---

**From:** Brown, Janice  
**Sent:** Monday, May 15, 2006 11:17 AM  
**To:** Rhee, H Julie  
**Subject:** RE: SoloStar supplements (for Lantus and Apidra)

Julie,  
In addition, please include a statement to review all information in section 3.2.P.7 Container Closure System which includes device components, specifications, methods, assembly process description.  
Janice

---

**From:** Rhee, H Julie  
**Sent:** Monday, May 15, 2006 11:09 AM  
**To:** Brown, Janice  
**Subject:** RE: SoloStar supplements (for Lantus and Apidra)

Thank you, Janice

I guess you want them to review accuracy and precision of the pen. Correct?

I am preparing a consult request now. When I am finished with them, I will enter them into DFS for your concurrence.

Thanks again,  
Julie

---

**From:** Brown, Janice  
**Sent:** Monday, May 15, 2006 11:08 AM  
**To:** Rhee, H Julie  
**Subject:** RE: SoloStar supplements (for Lantus and Apidra)

I think separate, but include a statement so they know that these supplements are related.  
Janice

**From:** Rhee, H Julie  
**Sent:** Monday, May 15, 2006 10:46 AM  
**To:** Brown, Janice  
**Subject:** RE: SoloStar supplements (for Lantus and Apidra)

Janice,

Do we need separate consult requests to CDRH )for Lantus and Apidra? Or could it be combined into one for both products?

Thanks,  
Julie

---

**From:** Brown, Janice  
**Sent:** Wednesday, May 10, 2006 12:00 PM  
**To:** Rhee, H Julie  
**Subject:** RE: SoloStar supplements (for Lantus and Apidra)

Julie,  
Please request a consult to review the device information supplied in section 3.2.P.7 Container Closure System. Device information includes information on the components of SoloStar® as well as the manufacturing and associated testing performed with assembled SoloStar.  
Janice

---

**From:** Rhee, H Julie  
**Sent:** Wednesday, May 10, 2006 10:45 AM  
**To:** Brown, Janice

**Subject:** FW: SoloStar supplements (for Lantus and Apidra)

Janice,

NDA number for Lantus is 21-081, not 21-801.

Thanks,  
Julie

---

**From:** Rhee, H Julie  
**Sent:** Wednesday, May 10, 2006 10:44 AM  
**To:** Brown, Janice  
**Subject:** SoloStar supplements (for Lantus and Apidra)

Hi Janice,

We have 2 supplements from Aventis for their new disposable insulin pen--Lantus SoloStar and Apidra SoloStar. They were submitted electronically to EDR.

I was planning to send a CDRH consult and wondering if you could help which part of the submission needs to be sent to CDRH and what would you like them to review.

The NDA numbers are NDA 21-801/S-024 and 21-629/S-008 and submission date is April 21, 2006.

Thanks,  
Julie

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/s/

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Janice Brown

5/15/2006 01:16:52 PM



NDA 21-629/S-008

**PRIOR APPROVAL SUPPLEMENT**

Sanofi-aventis U.S. LLC  
Attention: Chanda Walton, Ph.D.  
U.S. Regulatory Development  
300 Somerset Corporate Blvd  
Bridgewater, NJ 08807-0977

Dear Dr. Walton:

We have received your supplemental new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following:

Name of Drug Product: Apidra (insulin glulisine [rDNAorigin] injection)

NDA Number: 21-629

Supplement number: 008

Date of supplement: April 21, 2006

Date of receipt: April 24, 2006

This supplemental application proposes the following change: Addition of a new disposable insulin pen device, Apidra® SoloStar®.

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on June 23, 2006, in accordance with 21 CFR 314.101(a). If the application is filed, the user fee goal date will be August 24, 2006.

Please cite the application number listed above at the top of the first page of all submissions to this application. Send all submissions, electronic or paper, including those sent by overnight mail or courier, to the following address:

Food and Drug Administration  
Center for Drug Evaluation and Research  
Division of Metabolism and Endocrinology Products  
5901-B Ammendale Road  
Beltsville, MD 20705-1266

NDA 21-629/S-008

Page 2

If you have any question, call me at (301) 796-1280.

Sincerely,

*{See appended electronic signature page}*

Julie Rhee  
Regulatory Project Manager  
Division of Metabolism  
and Endocrinology Products  
Office of Drug Evaluation II  
Center for Drug Evaluation and Research

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/s/

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Julie Rhee

5/9/2006 03:29:09 PM

## REQUEST FOR CONSULTATION

TO (Division/Office):

**Director, Division of Medication Errors and  
Technical Support (DMETS), HFD-420  
WO22, RM 4447**

FROM: Julie Rhee, DMEP, WO 3368, 796-1280

DATE  
April 28, 2006

IND NO.

NDA NO.

21-629/S-008

TYPE OF DOCUMENT  
Original Supplement

DATE OF DOCUMENT  
April 21, 2006

NAME OF DRUG  
Apidra (insulin glulisine [rDNA  
origin] injection)

PRIORITY CONSIDERATION

CLASSIFICATION OF DRUG

DESIRED COMPLETION DATE  
August 10, 2006

NAME OF FIRM: Sanofi-Aventis

### REASON FOR REQUEST

#### I. GENERAL

- |  |  |   |
|--|--|---|
| <input type="checkbox"/> NEW PROTOCOL                  | <input type="checkbox"/> PRE--NDA MEETING        | <input type="checkbox"/> RESPONSE TO DEFICIENCY LETTER                              |
| <input type="checkbox"/> PROGRESS REPORT               | <input type="checkbox"/> END OF PHASE II MEETING | <input type="checkbox"/> FINAL PRINTED LABELING                                     |
| <input type="checkbox"/> NEW CORRESPONDENCE            | <input type="checkbox"/> RESUBMISSION            | <input type="checkbox"/> LABELING REVISION  |
| <input type="checkbox"/> DRUG ADVERTISING              | <input type="checkbox"/> SAFETY/EFFICACY         | <input type="checkbox"/> ORIGINAL NEW CORRESPONDENCE                                |
| <input type="checkbox"/> ADVERSE REACTION REPORT       | <input type="checkbox"/> PAPER NDA               | <input type="checkbox"/> FORMULATIVE REVIEW   |
| <input type="checkbox"/> MANUFACTURING CHANGE/ADDITION | <input type="checkbox"/> CONTROL SUPPLEMENT      | <input checked="" type="checkbox"/> OTHER (SPECIFY BELOW): <b>Trade name review</b> |
| <input type="checkbox"/> MEETING PLANNED BY            |  |   |

#### II. BIOMETRICS

STATISTICAL EVALUATION BRANCH

STATISTICAL APPLICATION BRANCH

- TYPE A OR B NDA REVIEW  
 END OF PHASE II MEETING  
 CONTROLLED STUDIES  
 PROTOCOL REVIEW  
 OTHER (SPECIFY BELOW):

- CHEMISTRY REVIEW  
 PHARMACOLOGY  
 BIOPHARMACEUTICS  
 OTHER (SPECIFY BELOW):

#### III. BIOPHARMACEUTICS

- |  |   |
|--|---|
| <input type="checkbox"/> DISSOLUTION             | <input type="checkbox"/> DEFICIENCY LETTER RESPONSE |
| <input type="checkbox"/> BIOAVAILABILITY STUDIES | <input type="checkbox"/> PROTOCOL-BIOPHARMACEUTICS  |
| <input type="checkbox"/> PHASE IV STUDIES        | <input type="checkbox"/> IN-VIVO WAIVER REQUEST     |

#### IV. DRUG EXPERIENCE

- |  |  |
|--|--|
| <input type="checkbox"/> PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL             | <input type="checkbox"/> REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY |
| <input type="checkbox"/> DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES | <input type="checkbox"/> SUMMARY OF ADVERSE EXPERIENCE                       |
| <input type="checkbox"/> CASE REPORTS OF SPECIFIC REACTIONS (List below)         | <input type="checkbox"/> POISON RISK ANALYSIS                                |
| <input type="checkbox"/> COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP       |  |

#### V. SCIENTIFIC INVESTIGATIONS

CLINICAL

PRECLINICAL

**COMMENTS/SPECIAL INSTRUCTIONS:**

This supplement provides for a new disposable insulin delivery device (SoloStar®) for use with Apidra. Please review whether or not the proposed tradename for the device, SoloStar, is acceptable. Also, please let me know if you have any labeling comments on the supplement. Since the submission is available in EDR, no paper copy of the submission is included with this consult request.

The sponsor submitted a separate supplement for the same device under NDA 21-081/S-024. I've filled out a consult request for that supplement as well. Thank you.

**PDUFA DATE: August 24, 2006**

NAME AND PHONE NUMBER OF REQUESTER

Julie Rhee

METHOD OF DELIVERY (Check one)

DFS ONLY

MAIL

HAND

SIGNATURE OF RECEIVER

SIGNATURE OF DELIVERER

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

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Julie Rhee  
4/28/2006 12:12:59 PM