



NDA 021081/S-073 and S-074  
NDA 021629/S-039 and S-040  
NDA 206538/S-013 and S-014

## SUPPLEMENT APPROVAL

Sanofi-aventis U.S. LLC  
Attention: HeiJen Sun, Ph.D. and Xin Chen, Ph.D.  
Director and Associate Director, Global Regulatory Affairs  
55 Corporate Drive  
Mail Stop: 55C-300  
Bridgewater, NJ 08807

Dear Dr. Sun and Dr. Chen:

Please refer to your supplemental new drug applications (sNDAs) dated and received as follows:

<b>NDA</b>	<b>Supplement</b>	<b>Drug name</b>	<b>Supplement Submitted and Received Date</b>
NDA 021081	S-073	Lantus (insulin glargine injection)	August 1, 2019
	S-074		October 3, 2019
NDA 021629	S-039	Apidra (insulin glulisine injection)	August 1, 2019
	S-040		October 4, 2019
NDA 206538	S-013	Toujeo (insulin glargine injection) U-300	July 31, 2019
	S-014		October 3, 2019

Please also refer your amendments, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Lantus, Apidra, and Toujeo. We also refer to our letter dated September 4, 2019, notifying you, under Section 505(o)(4) of the FDCA, of new safety information that we believe should be included in the labeling for injectable insulins. This information pertains to the risk of cutaneous amyloidosis.

NDA 021081/S-073, NDA 021629/S-039, and NDA 206538/S-013:

These Prior Approval supplemental new drug applications provide for updates to the Prescribing Information (PI) and carton labeling to specify that pens be dispensed in the original sealed carton, as requested in our June 20, 2019, Safety-Related Supplement

Request letters, and consistent with the comments sent to you in our October 10, 2019, correspondence.

NDA 021081/S-074, NDA 021629/S-040, and NDA 206538/S-014:

These supplemental new drug applications provide for revisions to the labeling consistent with our September 4, 2019, letter and the comments sent to you in our October 18 and 25, 2019, correspondence.

**APPROVAL & LABELING**

We have completed our review of these applications, as amended. They are approved, effective on the date of this letter, for use as recommended in the enclosed agreed-upon labeling with minor editorial revisions listed below and reflected in the enclosed labeling.

- Recent Major Changes dates have been updated, as warranted, to “11/2019” in the Highlights section of the Prescribing Information for Lantus, Apidra, and Toujeo.
- Revision dates have been updated to “11/2019” in the Highlights section of the Prescribing Information for Lantus, Apidra, and Toujeo.
- Approved/Revision dates have been updated to “November 2019” at the end of each Patient Information and Instructions for Use for Lantus, Apidra, and Toujeo.
- Copyright dates have been updated to “2019” in all pieces of labeling for Lantus, Apidra, and Toujeo, per emailed agreement dated November 1, 2019.
- In the Highlights section of the Apidra label, in the Warnings & Precautions section of Highlights, the word “glucose” was restored (inserted between the words “blood” and “monitoring”) near the end of the second bullet point titled *Hyperglycemia or Hypoglycemia with Changes in Insulin Regimen*, per emailed agreement dated November 11, 2019.

**WAIVER OF ½ PAGE LENGTH REQUIREMENT FOR TOUJEO HIGHLIGHTS**

Please note that we have previously granted a waiver of the requirements of 21 CFR 201.57(d)(8) regarding the length of the Toujeo Highlights of Prescribing Information.

## **CONTENT OF LABELING**

As soon as possible, but no later than 14 days from the date of this letter, submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format using the FDA automated drug registration and listing system (eLIST), as described at FDA.gov.<sup>1</sup> Content of labeling must be identical to the enclosed labeling (text for the Prescribing Information, Patient Package Insert, and Instructions for Use), with the addition of any labeling changes in pending “Changes Being Effected” (CBE) supplements, as well as annual reportable changes not included in the enclosed labeling.

Information on submitting SPL files using eList may be found in the guidance for industry *SPL Standard for Content of Labeling Technical Qs and As*.<sup>2</sup>

The SPL will be accessible from publicly available labeling repositories.

Also within 14 days, amend all pending supplemental applications that include labeling changes for this NDA, including CBE supplements for which FDA has not yet issued an action letter, with the content of labeling [21 CFR 314.50(l)(1)(i)] in Microsoft Word format, that includes the changes approved in this supplemental application, as well as annual reportable changes. To facilitate review of your submission(s), provide a highlighted or marked-up copy that shows all changes, as well as a clean Microsoft Word version. The marked-up copy should provide appropriate annotations, including supplement number(s) and annual report date(s).

## **CARTON AND CONTAINER LABELING**

Submit final printed carton and container labeling that are identical to the enclosed carton and container labeling and carton and container labeling submitted on August 8, 2019, as soon as they are available, but no more than 30 days after they are printed. Please submit these labeling electronically according to the guidance for industry *Providing Regulatory Submissions in Electronic Format — Certain Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications*. For administrative purposes, designate these submissions “**Final Printed Carton and Container Labeling for approved NDA 021081/S-073 and S-074,**” “**Final Printed Carton and Container Labeling for approved NDA 021629/S-039 and S-040,**” or “**Final Printed Carton and Container Labeling for approved NDA 206538/S-013 and S-014.**” Approval of this submission by FDA is not required before the labeling is used.

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<sup>1</sup> <http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm>

<sup>2</sup> We update guidances periodically. For the most recent version of a guidance, check the FDA Guidance Documents Database <https://www.fda.gov/RegulatoryInformation/Guidances/default.htm>.

## **REQUIRED PEDIATRIC ASSESSMENTS**

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients (which includes new salts and new fixed combinations), new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Because none of these criteria apply to your supplemental applications, you are exempt from this requirement.

## **PROMOTIONAL MATERIALS**

You may request advisory comments on proposed introductory advertising and promotional labeling. To do so, submit the following, in triplicate, (1) a cover letter requesting advisory comments, (2) the proposed materials in draft or mock-up form with annotated references, and (3) the Prescribing Information to:

OPDP Regulatory Project Manager  
Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Prescription Drug Promotion (OPDP)  
5901-B Ammendale Road  
Beltsville, MD 20705-1266

Alternatively, you may submit a request for advisory comments electronically in eCTD format. For more information about submitting promotional materials in eCTD format, see the draft guidance for industry *Providing Regulatory Submissions in Electronic and Non-Electronic Format-Promotional Labeling and Advertising Materials for Human Prescription Drugs*.<sup>3</sup>

You must submit final promotional materials and Prescribing Information, accompanied by a Form FDA 2253, at the time of initial dissemination or publication [21 CFR 314.81(b)(3)(i)]. Form FDA 2253 is available at FDA.gov.<sup>4</sup> Information and Instructions for completing the form can be found at FDA.gov.<sup>5</sup> For more information

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<sup>3</sup> When final, this guidance will represent the FDA's current thinking on this topic. For the most recent version of a guidance, check the FDA guidance web page at <https://www.fda.gov/RegulatoryInformation/Guidances/default.htm>.

<sup>4</sup> <http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM083570.pdf>

<sup>5</sup> <http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM375154.pdf>

about submission of promotional materials to the Office of Prescription Drug Promotion (OPDP), see FDA.gov.<sup>6</sup>

All promotional materials that include representations about your drug product must be promptly revised to be consistent with the labeling changes approved in this supplement, including any new safety information [21 CFR 314.70(a)(4)]. The revisions in your promotional materials should include prominent disclosure of the important new safety information that appears in the revised labeling. Within 7 days of receipt of this letter, submit your statement of intent to comply with 21 CFR 314.70(a)(4) to the address above, by fax to 301-847-8444, or electronically in eCTD format. For more information about submitting promotional materials in eCTD format, see the draft guidance for industry *Providing Regulatory Submissions in Electronic and Non-Electronic Format-Promotional Labeling and Advertising Materials for Human Prescription Drugs*.

## **REPORTING REQUIREMENTS**

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

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<sup>6</sup> <http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm>

If you have any questions, call Michael G. White, Ph.D., Senior Regulatory Project Manager, at (240) 402-6149.

Sincerely,

*{See appended electronic signature page}*

Anil Rajpal, M.D., M.P.H.  
Deputy Director for Safety (Acting)  
Division of Metabolism and Endocrinology Products  
Office of Drug Evaluation II  
Center for Drug Evaluation and Research

ENCLOSURES:

Lantus

- Content of Labeling
  - Prescribing Information
  - Vial presentation Patient Package Insert
  - Vial presentation Instructions for Use
  - SoloStar Patient Package Insert
  - SoloStar Instructions for Use
- Carton and Container Labeling

Apidra

- Content of Labeling
  - Prescribing Information
  - Patient Package Insert
  - Vial presentation Instructions for Use
  - SoloStar Instructions for Use
- Carton and Container Labeling

Toujeo

- Content of Labeling
  - Prescribing Information
  - Patient Package Insert
  - SoloStar Instructions for Use
  - Max SoloStar Instructions for Use
- Carton and Container Labeling

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**This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.**  
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/s/  
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ANIL K RAJPAL  
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