NDA 020986/S-090
NDA 020986/S-091
NDA 021810/S-018
NDA 021810/S-019
NDA 021172/S-071
NDA 021172/S-072

**SUPPLEMENT APPROVAL**

Novo Nordisk Inc.
Attention: Elizabeth D'Amato
Director, Regulatory Affairs
P.O. Box 846
800 Scudders Mill Rd
Plainsboro, NJ 08536

Dear Ms. D'Amato:

Please refer to the following supplemental new drug applications (sNDAs) and amendments, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA):

| Trade | Established | NDA/S# | Submission Date |
|---|---|---|---|
| Novolog | (insulin aspart) | 20986/S-090 | July 31, 2019 |
| Novolog | (insulin aspart) | 20986/S-091 | October 3, 2019 |
| Novolog Mix 50/50 | (insulin aspart protamine and insulin aspart) | 21810/S-018 | July 31, 2019 |
| Novolog Mix 50/50 | (insulin aspart protamine and insulin aspart) | 21810/S-019 | October 3, 2019 |
| Novolog Mix 70/30 | (insulin aspart protamine and insulin aspart) | 21172/S-071 | July 31, 2019 |
| Novolog Mix 70/30 | (insulin aspart protamine and insulin aspart) | 21172/S-072 | October 3, 2019 |

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.

S-090, S-018, S-071: 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 letter and consistent with the comments sent to you in our October 10, 2019, correspondence.

S-091, S-019, S-072: 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 23, 2019, and November 5, 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.

- In the Patient Package Insert for Novolog Mix 70/30 the phrase 'injections site' was changed to 'injection sites' and a period was added to the bullet below.

## WAIVER OF ½ PAGE LENGTH REQUIREMENT FOR HIGHLIGHTS

Please note that we have previously granted a waiver of the requirements of 21 CFR 201.57(d)(8) regarding the length of Highlights of Prescribing Information for Novolog Mix 50/50.

## 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.[1] 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*.[2]

[1] http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm
[2] 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.

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 LABELING

Submit final printed carton labeling that are identical to the enclosed carton labeling, 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 this submission "**Final Printed Carton and Container Labeling for approved NDA ######/S-###**." Approval of this submission by FDA is not required before the labeling is used.

## 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 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.*[3]

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.[4] Information and Instructions for completing the form can be found at FDA.gov.[5] For more information about submission of promotional materials to the Office of Prescription Drug Promotion (OPDP), see FDA.gov.[6]

[3] 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.

[4] http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM083570.pdf
[5] http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM375154.pdf
[6] http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm

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).

If you have any questions, call Callie Cappel-Lynch, Regulatory Project Manager, at (301) 796-8436.

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:

- Novolog Content of Labeling
  - Prescribing Information
  - Patient Package Insert
  - Instructions for Use
- Novolog Carton Labeling
- Novolog Mix 50/50 Content of Labeling
  - Prescribing Information

    - Patient Package Insert
    - Instructions for Use
- Novolog Mix 50/50 Carton Labeling
- Novolog Mix 70/30 Content of Labeling
    - Prescribing Information
    - Patient Package Insert
    - Instructions for Use
- Novolog Mix 70/30 Carton Labeling

---

**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.**

---

/s/

---

ANIL K RAJPAL
11/15/2019 10:50:40 AM