DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

BLA 125504/0

BLA APPROVAL

Novartis Pharmaceuticals Corporation
Attention: Katie Picone, PharmD
Director, Drug Regulatory Affairs
One Health Plaza
Building 135, Office 414
East Hanover, NJ 07936-1080

Dear Dr. Picone:

Please refer to your Biologics License Application (BLA) dated October 24, 2013, received October 24, 2013, submitted under section 351(a) of the Public Health Service Act for COSENTYX™ (secukinumab).

We acknowledge receipt of your amendments dated November 12, December 20 and 23, 2013; January 15, 30 and 31, February 6, 12 and 20, March 12, April 4 (2), May 28, June 9, 11 (2) and 30, July 2, 14, 21, 23 and 31 (2), August 4, 8, 12, 13, 19 and 25, September 3 (2) and 17, October 10, 17 and 24, November 10 and 20, December 4, 9, 10, 15, 17, 19 and 23, 2014; January 8, 15, 16 (2) and 20, 2015.

LICENSING

We have approved your BLA for COSENTYX™ (secukinumab) effective this date. You are hereby authorized to introduce or deliver for introduction into interstate commerce, COSENTYX™ under your existing Department of Health and Human Services U.S. License No. 1244. COSENTYX™ is indicated for the treatment of moderate to severe plaque psoriasis in adult patients who are candidates for systemic therapy or phototherapy.

MANUFACTURING LOCATIONS

Under this license, you are approved to manufacture secukinumab drug substance at Novartis Pharma S.A.S. Centre de Biotechnologie in Huningue, France. The final formulated product will be manufactured, filled, labeled, and packaged at Novartis Pharma Stein AG, 4332-Stein, Switzerland (primary and secondary packaging) and (b) (4) (secondary packaging). You may label your product with the proprietary name, COSENTYX™, and market it in a single use prefilled syringe (PFS) or autoinjector (AI) containing 150 mg secukinumab, in a 1 ml solution, and in a single use vial containing 150 mg lyophilized powder for injection.

DATING PERIOD

The dating period for COSENTYX™ shall be 36 months from the date of manufacture for the lyophilized vial and 24 months from the date of manufacture for the PFS and AI when stored at 5° ± 3°C. The date of manufacture shall be defined [redacted] The dating period for your drug substance shall be [redacted] months from the date of manufacture when stored [redacted]

We have approved the stability protocols in your license application for the purpose of extending the expiration dating period of your drug substance and drug product under 21 CFR 601.12.

FDA LOT RELEASE

You are not currently required to submit samples of future lots of COSENTYX™ to the Center for Drug Evaluation and Research (CDER) for release by the Director, CDER, under 21 CFR 610.2. We will continue to monitor compliance with 21 CFR 610.1, requiring completion of tests for conformity with standards applicable to each product prior to release of each lot.

Any changes in the manufacturing, testing, packaging, or labeling of COSENTYX™, or in the manufacturing facilities, will require the submission of information to your biologics license application for our review and written approval, consistent with 21 CFR 601.12.

APPROVAL & LABELING

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, submit, via the FDA automated drug registration and listing system (eLIST), the content of labeling [21 601.14(b)] in structured product labeling (SPL) format, as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm. Content of labeling must be identical to the enclosed labeling (text for the package insert, Medication Guide, Instructions for Use). Information on submitting SPL files using eLIST may be found in the guidance for industry titled "SPL Standard for Content of Labeling Technical Qs and As" at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf.

The SPL will be accessible via publicly available labeling repositories.

CARTON AND IMMEDIATE CONTAINER LABELS

Submit final printed carton and container labels that are identical to the enclosed carton and immediate container labels 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 (June 2008)". 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 "**Product Correspondence – Final Printed Carton and Container Labels for approved BLA 125504/0**." Approval of this submission by FDA is not required before the labeling is used.

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

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, 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(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

We are waiving the pediatric study requirement for ages 0 to less than 6 years because necessary studies are impossible or highly impracticable. This is because:

- The prevalence of psoriasis in the 0 to less than 6 years age group is low (with the highest prevalence published of 0.3%) and the proportion of children with a severe condition in need of a systemic treatment is 4%, giving a final prevalence of the condition to be about 1 per 10,000 in this age group.
- Live vaccinations (MMR, varicella) are usually given in this age group, limiting the treatment of this pediatric population with secukinumab.

We are deferring submission of your pediatric study for ages 6 to 17 years for this application because pediatric studies should be delayed until additional safety or effectiveness data have been collected. Serious safety signals have been observed in clinical trials for biologic agents in adult patients with arthritis, inflammatory bowel disease and psoriasis, and the Agency has determined that pediatric studies should be deferred until after adult studies have been completed and additional safety data are collected and reviewed for adult psoriasis patients.

Your deferred pediatric study required by section 505B(a) of the Federal Food, Drug, and Cosmetic Act (FDCA) is a required postmarketing study. The status of this postmarketing study must be reported annually according to 21 CFR 601.28 and section 505B(a)(3)(B) of the Federal Food, Drug, and Cosmetic Act. This required study is listed below.

2848-1 Conduct a study to evaluate the safety and efficacy of secukinumab in pediatric subjects ≥ 6 years of age with plaque psoriasis.

Final Protocol Submission:	01/2022
Study Completion:	12/2025

Final Report Submission: 02/2026

Submit the protocol to your IND 100418, with a cross-reference letter to this BLA.

Reports of this required pediatric postmarketing study must be submitted as a BLA or as a supplement to your approved BLA with the proposed labeling changes you believe are warranted based on the data derived from this study. When submitting the reports, please clearly mark your submission "**SUBMISSION OF REQUIRED PEDIATRIC ASSESSMENTS**" in large font, bolded type at the beginning of the cover letter of the submission.

POSTMARKETING REQUIREMENTS UNDER 505(o)

Section 505(o)(3) of the Federal Food, Drug, and Cosmetic Act (FDCA) authorizes FDA to require holders of approved drug and biological product applications to conduct postmarketing studies and clinical trials for certain purposes, if FDA makes certain findings required by the statute.

We have determined that an analysis of spontaneous postmarketing adverse events reported under subsection 505(k)(1) of the FDCA will not be sufficient to assess a signal of a serious risk of malignancy which occurs infrequently and/or has a long latency.

Furthermore, the new pharmacovigilance system that FDA is required to establish under section 505(k)(3) of the FDCA will not be sufficient to assess this serious risk.

Therefore, based on appropriate scientific data, FDA has determined that you are required to conduct the following:

2848-2 A postmarketing prospective, long-term, observational study to assess the long-term safety of secukinumab compared to other therapies used in the treatment of adults with moderate to severe plaque psoriasis who are candidates for systemic therapy or phototherapy in a real world clinical setting. The study's primary outcome is malignancies. Describe and justify the choice of appropriate comparator population(s). Design the study around a testable hypothesis to assess, with sufficient sample size and power, a clinically meaningful increase in malignancy risk above the comparator background rate. Specify concise case definitions and validation algorithms for the primary outcome. Enroll patients over an initial 4-year period and follow for a minimum of 8 years from the time of enrollment. Provide progress updates on registry patient accrual and demographic summary data in your Annual Report, and provide registry safety data in your Periodic Benefit-Risk Evaluation Reports (PBERs) for the reporting period as well as cumulatively, and a complete final study report.

The timetable you submitted on January 16, 2015, states that you will conduct this study according to the following schedule:

Protocol Submission:	03/2015
Interim Study Report Submission:	06/2027
Study Completion:	06/2029
Final Report Submission:	06/2030

Finally, we have determined that only a clinical trial (rather than a nonclinical or observational study) will be sufficient to assess signals of the serious risks of serious infection, tuberculosis, opportunistic infections, malignancy, hypersensitivity reactions, autoimmune disease, neurologic or demyelinating disease, cardiovascular, gastrointestinal or hematologic adverse events.

2848-3 Complete the treatment and evaluation of subjects enrolled in the ongoing CAIN457A2302E1 trial for a duration of 4 years, unless a safety signal is identified that indicates the potential risks of such continued long-term treatment outweigh the benefits. Evaluation of subjects should continue through the end of the trial when achievable (even if treatment is not continued for the duration). Subjects will be followed for the occurrence of serious infection, tuberculosis, opportunistic infections, malignancy, hypersensitivity reactions, autoimmune disease, neurologic or demyelinating disease, cardiovascular, gastrointestinal or hematologic adverse events.

The timetable you submitted on December 15, 2014, states that you will conduct these trials according to the following schedule:

Trial Completion:	09/2017
Final Report Submission:	09/2018

2848-4 Complete the treatment and evaluation of subjects enrolled in the ongoing CAIN457A2304E1 trial for a duration of 4 years, unless a safety signal is identified that indicates the potential risks of such continued long-term treatment outweigh the benefits. Evaluation of subjects should continue through the end of the trial when achievable (even if treatment is not continued for the duration). Subjects will be followed for the occurrence of serious infection, tuberculosis, opportunistic infections, malignancy, hypersensitivity reactions, autoimmune disease, neurologic or demyelinating disease, cardiovascular, gastrointestinal or hematologic adverse events.

Trial Completion:	07/2017
Final Report Submission:	07/2018

Submit all final reports to your BLA. Prominently identify the submission with the following wording in bold capital letters at the top of the first page of the submission, as appropriate: **"Required Postmarketing Protocol Under 505(o)", "Required Postmarketing Final Report Under 505(o)", "Required Postmarketing Correspondence Under 505(o)"**.

Section 505(o)(3)(E)(ii) of the FDCA requires you to report periodically on the status of any study or clinical trial required under this section. This section also requires you to periodically report to FDA on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Section 506B of the FDCA, as well as 21 CFR 601.70 requires you to report annually on the status of any postmarketing commitments or required studies or clinical trials.

FDA will consider the submission of your annual report under section 506B and 21 CFR 601.70 to satisfy the periodic reporting requirement under section 505(o)(3)(E)(ii) provided that you include the elements listed in 505(o) and 21 CFR 601.70. We remind you that to comply with 505(o), your annual report must also include a report on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Failure to submit an annual report for studies or clinical trials required under 505(o) on the date required will be considered a violation of FDCA section 505(o)(3)(E)(ii) and could result in enforcement action.

POSTMARKETING COMMITMENTS SUBJECT TO REPORTING REQUIREMENTS UNDER SECTION 506B

We remind you of your postmarketing commitments:

2848-5 Conduct a clinical trial to assess whether secukinumab alters the metabolism or pharmacokinetics of CYP substrates in psoriasis patients treated with secukinumab.

The timetable you submitted on October 10, 2014 states that you will conduct this trial according to the following schedule:

Final Protocol Submission:	04/2015
Trial Completion:	11/2015
Final Report Submission:	05/2016

2848-6 Conduct a clinical trial to evaluate the treatment effect and safety profile of a higher exposure (e.g., 450 mg) of secukinumab in psoriasis subjects with higher body weight and to explore the option of exposure escalation (e.g., 450 mg) for those who cannot achieve the therapeutic goal at the 300 mg dose.

The timetable you submitted on December 15, 2014 states that you will conduct this trial according to the following schedule:

Final Protocol Submission:	11/2015
Trial Completion:	07/2022
Final Report Submission:	07/2023

POSTMARKETING COMMITMENTS NOT SUBJECT TO THE REPORTING REQUIREMENTS UNDER SECTION 506B

We remind you of your postmarketing commitments:

2848-7 Re-evaluate secukinumab drug substance lot release and stability specifications after 30 lots have been manufactured using the commercial manufacturing process. Novartis will submit the corresponding data, the analytical and statistical plan used to evaluate the specifications, and any proposed changes to the specifications.

The timetable you submitted on October 10, 2014, states that you will conduct this study according to the following schedule:

Final Report Submission: 12/2018

2848-8 Re-evaluate secukinumab drug product (vial) lot release and stability specifications after 30 lots have been manufactured using the commercial manufacturing process. Novartis will submit the corresponding data, the analytic and statistical plan used to evaluate the specifications, and any proposed changes to the specifications.

The timetable you submitted on October 10, 2014, states that you will conduct this study according to the following schedule:

Final Report Submission: 12/2019

2848-9 Re-evaluate secukinumab drug product (prefilled syringe) lot release and stability specifications after 30 lots have been manufactured using the commercial manufacturing process. Novartis will submit the corresponding data, the analytic and statistical plan used to evaluate the specifications, and any proposed changes to the specifications.

The timetable you submitted on October 10, 2014, states that you will conduct this study according to the following schedule:

Final Report Submission: 12/2017

2848-10 Conduct routine bioburden testing (b) (4) The bioburden method will be qualified with samples from the next production batches in 2015. Routine testing will be implemented for the 2016 manufacturing campaign.

The timetable you submitted on October 10, 2014, states that you will conduct this study according to the following schedule:

Final Report Submission: 12/2015 (method qualification report)
08/2016 (evidence of implementation of test)

2848-11 Conduct routine bioburden testing [redacted] (b) (4) The bioburden method will be qualified with samples from the next production batches in 2015. Routine testing will be implemented for the 2016 manufacturing campaign.

The timetable you submitted on October 10, 2014, states that you will conduct this study according to the following schedule:

Final Report Submission: 12/2015 (method qualification report)
08/2016 (evidence of implementation of test)

2848-12 Conduct routine bioburden and endotoxin testing [redacted] (b) (4) Routine testing will be implemented for the 2015 manufacturing campaign.

The timetable you submitted on October 10, 2014, states that you will conduct this study according to the following schedule:

Final Report Submission: 03/2015 (evidence of implementation of test)

2848-13 Conduct additional hold time validation studies on two batches at commercial scale [redacted] (b) (4) validation will be conducted during the 2015 and 2016 commercial campaigns.

The timetable you submitted on October 10, 2014, states that you will conduct this study according to the following schedule:

Final Report Submission: 06/2016

2848-14 Evaluate feasibility of [redacted] (b) (4) secukinumab drug substance and update drug substance specification [redacted] (b) (4)

The timetable you submitted on October 10, 2014, states that you will conduct this study according to the following schedule:

Final Report Submission: 03/2015 (report of the evaluation conducted)

Submit clinical protocols to your IND 100418 for this product. Submit nonclinical and chemistry, manufacturing, and controls protocols and all postmarketing final reports to this BLA. In addition, under 21 CFR 601.70 you should include a status summary of each commitment in your annual progress report of postmarketing studies to this BLA. The status summary should include expected summary completion and final report submission dates, any changes in plans since the last annual report, and, for clinical studies/trials, number of patients entered into each study/trial. All submissions, including supplements, relating to these postmarketing commitments should be prominently labeled "**Postmarketing Commitment Protocol**," "**Postmarketing Commitment Final Report**," or "**Postmarketing Commitment Correspondence**."

RISK EVALUATION AND MITIGATION STRATEGY REQUIREMENTS

We acknowledge receipt of your submission dated October 24, 2013, of a proposed risk evaluation and mitigation strategy (REMS). We have determined that, at this time, a REMS is not necessary for COSENTYX™ (secukinumab) to ensure that its benefits outweigh its risks. We will notify you if we become aware of new safety information and make a determination that a REMS is necessary.

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 to:

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion
5901-B Ammendale Road
Beltsville, MD 20705-1266

As required under 21 CFR 601.12(f)(4), you must submit final promotional materials, and the package insert, at the time of initial dissemination or publication, accompanied by a Form FDA 2253. Form FDA 2253 is available at http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM083570.pdf. Information and Instructions for completing the form can be found at http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM375154.pdf. For more information about submission of promotional materials to the Office of Prescription Drug Promotion (OPDP), see http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm.

REPORTING REQUIREMENTS

You must submit adverse experience reports under the adverse experience reporting requirements for licensed biological products (21 CFR 600.80). You should submit postmarketing adverse experience reports to:

Food and Drug Administration
Center for Drug Evaluation and Research
Central Document Room
5901-B Ammendale Road
Beltsville, MD 20705-1266

Prominently identify all adverse experience reports as described in 21 CFR 600.80.

You must submit distribution reports under the distribution reporting requirements for licensed biological products (21 CFR 600.81).

You must submit reports of biological product deviations under 21 CFR 600.14. You should promptly identify and investigate all manufacturing deviations, including those associated with processing, testing, packing, labeling, storage, holding and distribution. If the deviation involves a distributed product, may affect the safety, purity, or potency of the product, and meets the other criteria in the regulation, you must submit a report on Form FDA-3486 to:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Compliance Risk Management and Surveillance
5901-B Ammendale Road
Beltsville, MD 20705-1266

Biological product deviations, sent by courier or overnight mail, should be addressed to:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Compliance Risk Management and Surveillance
10903 New Hampshire Avenue, Bldg. 51, Room 4206
Silver Spring, MD 20903

MEDWATCH-TO-MANUFACTURER PROGRAM

The MedWatch-to-Manufacturer Program provides manufacturers with copies of serious adverse event reports that are received directly by the FDA. New molecular entities and important new biologics qualify for inclusion for three years after approval. Your firm is eligible to receive copies of reports for this product. To participate in the program, please see the enrollment instructions and program description details at http://www.fda.gov/Safety/MedWatch/HowToReport/ucm166910.htm.

POST APPROVAL FEEDBACK MEETING

New molecular entities and new biologics qualify for a post approval feedback meeting. Such meetings are used to discuss the quality of the application and to evaluate the communication process during drug development and marketing application review. The purpose is to learn from successful aspects of the review process and to identify areas that could benefit from

improvement. If you would like to have such a meeting with us, call the Regulatory Project Manager for this application.

PDUFA V APPLICANT INTERVIEW

FDA has contracted with Eastern Research Group, Inc. (ERG) to conduct an independent interim and final assessment of the Program for Enhanced Review Transparency and Communication for NME NDAs and Original BLAs under PDUFA V ('the Program'). The PDUFA V Commitment Letter states that these assessments will include interviews with applicants following FDA action on applications reviewed in the Program. For this purpose, first-cycle actions include approvals, complete responses, and withdrawals after filing. The purpose of the interview is to better understand applicant experiences with the Program and its ability to improve transparency and communication during FDA review.

ERG will contact you to schedule a PDUFA V applicant interview and provide specifics about the interview process. Your responses during the interview will be confidential with respect to the FDA review team. ERG has signed a non-disclosure agreement and will not disclose any identifying information to anyone outside their project team. They will report only anonymized results and findings in the interim and final assessments. Members of the FDA review team will be interviewed by ERG separately. While your participation in the interview is voluntary, your feedback will be helpful to these assessments.

If you have any questions, call Matthew White, Senior Regulatory Project Manager, at (301) 796-4997.

Sincerely,

{See appended electronic signature page}

Amy G. Egan, MD, MPH
Deputy Director
Office of Drug Evaluation III
Center for Drug Evaluation and Research

ENCLOSURES:
Content of Labeling
Carton and Container Labeling

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

/s/

AMY G EGAN
01/21/2015