DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

BLA 125319/62

SUPPLEMENT APPROVAL
NEW POSTMARKETING REQUIREMENT/COMMITMENT

Novartis Pharmaceuticals Corporation
One Health Plaza
East Hanover, NJ 07936-1080

Attention: Jiten Rana, Pharm. D.
Manager, Drug Regulatory Affairs

Dear Dr. Rana:

Please refer to your Supplemental Biologics License Application (sBLA), dated October 30, 2012, and received November 7, 2012, submitted under section 351(a) of the Public Health Service Act for Ilaris (canakinumab).

We acknowledge receipt of your amendments dated January 14, 15 and 17, February 7, 21 and 28, March 6 and 28, and April 26 and 29, and May 2, 3, 6, 7, and 8, 2013.

This Prior Approval supplemental biologics application provides for the treatment of Systemic Juvenile Idiopathic Arthritis (SJIA) in patients aged 2 years and older.

We have completed our review of this supplemental 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 CFR 601.14(b)] in structured product labeling (SPL) format, as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm, that is identical to the enclosed labeling text for the package insert and text for the Medication Guide and include the labeling changes proposed in any pending "Changes Being Effected" (CBE) supplements. 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.

Also within 14 days, amend all pending supplemental applications that includes labeling changes for this BLA, including pending "Changes Being Effected" (CBE) supplements, for which FDA has not yet issued an action letter, with the content of labeling [21 CFR 601.12(f)] in MS Word format that includes the changes approved in this supplemental application.

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.

Because this drug product for this indication has an orphan drug designation, you are exempt from this requirement.

POSTMARKETING COMMITMENTS SUBJECT TO REPORTING REQUIREMENTS UNDER SECTION 506B

We remind you of your postmarketing commitment:

1. Develop a validated, sensitive, and accurate assay for the detection of anti-drug antibodies (ADA), including procedures for the detection of ADA in the presence of canakinumab levels that are expected to be present in the sera of patients at the time of sample collection. This assay should be used to assess ADA in patient samples banked from the pivotal trials, if available, and on-going clinical trials.

The timetable you submitted on May 2, 2013, states that you will conduct this study according to the following schedule:

Final Report Submission: September 2014

Submit clinical protocols to your IND 100040 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**."

POSTMARKETING REQUIREMENTS UNDER 505(o)

Section 505(o)(3) of the 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.

Ilaris (canakinumab) was approved on June 17, 2009, for adults and children 4 years and older with cryopyrin associated periodic syndromes (CAPS). Since Ilaris (canakinumab) was approved, we have become aware of events of serious infections, neutropenia, thrombocytopenia, and severe injection site reactions in clinical trials of adults in other indications. In clinical trials of pediatric patients with Systemic JIA (SJIA), events of macrophage activation syndrome (MAS) were observed. The pediatric clinical trials in patients with SJIA comprise a relatively limited safety database, therefore the risks of serious infections, neutropenia, thrombocytopenia, severe injection site reactions, and MAS need to be defined in this pediatric population. In addition, since the long-term risks of Ilaris (canakinumab) in pediatric patients with SJIA are unknown and these patients will require chronic treatment, further investigation of the long-term safety of Ilaris (canakinumab) is essential. We consider this information to be "new safety information" as defined in section 505-1(b)(3) of the FDCA.

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 the signal of a serious risk of serious infection, neutropenia, thrombocytopenia, severe injection site reactions, and MAS with long-term Ilaris (canakinumab) treatment.
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:

2. A long-term safety study in 100 pediatric patients 2 to 17 years of age with systemic JIA (SJIA) treated with canakinumab to evaluate for the risks of serious infections, neutropenia, thrombocytopenia, severe injection site reactions, and MAS. The study should include a control group of SJIA patients not receiving canakinumab. Patients should be followed for 5 years.

The timetable you submitted on April 29, 2013, states that you will conduct this study according to the following schedule:

Final Protocol Submission:	October 2013
Study Completion:	June 2022
Final Report Submission:	June 2023

Submit the protocol(s) to your IND 100040, with a cross-reference letter to this BLA. Submit all final report(s) 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.

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
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(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 Office of Prescription Drug Promotion (OPDP), see http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm.

REPORTING REQUIREMENTS

We remind you that you must comply with reporting requirements for an approved BLA (in 21 CFR 600.80 and in 21 CFR 600.81).

If you have any questions, call Carol F. Hill, Senior Regulatory Health Project Manager, at (301) 796-1226.

Sincerely,

{See appended electronic signature page}

Badrul A. Chowdhury, M.D., Ph.D.
Director
Division of Pulmonary, Allergy, and Rheumatology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

ENCLOSURE:
Content of Labeling

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

/s/

BADRUL A CHOWDHURY
05/09/2013