DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

Our STN: BLA 125319

BLA APPROVAL
June 17, 2009

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

Attention: Frederick De Brito, PhD
Associate Director, Drug Regulatory Affairs

Dear Dr. De Brito:

Please refer to your biologics license application (BLA) dated December 15, 2008, received December 17, 2008, submitted under section 351 of the Public Health Service Act for Ilaris (canakinumab).

We acknowledge receipt of your submissions dated January 14, February 3, 5, 6, 9, 11(4), 12, 19, 20, and 27, March 9, 13(3), 20, and 31, April 1, 6, 8, 9, 15, 17, 27(2), and 29, and May 1, 5, 15(2), 18(2), 20, and 27, and June 8, 2009.

We have approved your biologics license application for Ilaris (canakinumab) effective this date, June 17, 2009. You are hereby authorized to introduce or deliver for introduction into interstate commerce Ilaris (canakinumab) under your existing Department of Health and Human Services U.S. License No. 1244. Ilaris (canakinumab) is indicated for the treatment of Cryopyrin-Associated Periodic Syndromes (CAPS).

Your application for Ilaris (canakinumab) was not referred to an FDA advisory committee because your product is a member of the class of interleukin (IL)-1 blockers, and the safety and efficacy data did not pose unique concerns beyond those applicable to the already approved biologic products in the IL-1 blocker class for the treatment of CAPS.

Under this license, you are approved to manufacture canakinumab drug substance at your Novartis Pharma, S.A.S., Huningue, France, facility. The final lyophilized drug product will be manufactured, labeled, and packaged at the Novartis Pharma, AG, Stein, Switzerland, facility. You may label your product with the proprietary name Ilaris and market it in 6-mL, single-use vials, each containing 180 mg of canakinumab.

The expiration dating period for Ilaris (canakinumab) shall be 15 months from the date of manufacture when stored at 2° to 8°C. The date of manufacture shall be defined as the date of (b) (4) of the formulated drug product. The dating period for your drug substance shall be 18 months when stored at ≤ -60°C.

You currently are not required to submit samples of future lots of Ilaris (canakinumab) 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.

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 in pediatric patients unless this requirement is waived, deferred, or inapplicable.

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

POSTMARKETING REQUIREMENTS UNDER 505(o)

Section 505(o) 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 (section 505(o)(3)(A)).

During review of the BLA, it was noted that the current Working Cell Bank was manufactured using (b) (4) sources. It was assessed that the risk for transmissible spongiform encephalopathy (TSE) was extremely low and that this should not prevent approval of the BLA. However, to further reduce the very low risk of possible TSE transmission, the FDA has determined that a new working cell bank using U.S.-licensed human serum albumin must be established and used for the manufacture of all future canakinumab lots.

Additionally, we noted during the review of safety data in BLA 125319 that there were insufficient clinical data to determine the safety of higher doses of Ilaris (canakinumab), i.e., 4 mg/kg subcutaneously for patients weighing 15 to 40 kg or 300 mg subcutaneously for patients weighing >40 kg, when patients from these weight groups were not responding to the doses of 2 mg/kg or 150 mg subcutaneously, respectively.

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 identify an unexpected serious risk of transmissible spongiform encephalopathy (TSE) that could be associated with use of human serum albumin sourced from non-U.S.-licensed sources or to identify an unexpected serious risk of higher doses of Ilaris (canakinumab).

Furthermore, the new pharmacovigilance system that FDA is required to establish under section 505(k)(3) of the FDCA has not yet been established and is not sufficient to identify these serious risks.

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

1. Develop a study protocol for establishing new working cell banks using human serum albumin obtained from a U.S.-licensed source. The protocol should include acceptance criteria for cell culture metrics and canakinumab quality attributes, and provide limits that assure that validated cell generation time from the Master Cell Bank will be maintained.

   The timetable you submitted on June 15, 2009, states that you will conduct this study according to the following timetable:

Final Protocol Submission:	February 2010
New Working Cell Bank Established	July 2010
Final Report submission	July 2010

Finally, we have determined that only a clinical trial (rather than a nonclinical or observational study) will be sufficient to identify an unexpected serious risk associated with use of Ilaris (canakinumab) at higher doses and in the weight groups indicated above.

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

2. Complete and report the ongoing, open-label, clinical trial D2306 investigating the safety of higher doses of Ilaris (canakinumab). Patients in trial D2306 who are non-responders to 2 mg/kg subcutaneously for patients weighing 15 to 40 kg or 150 mg subcutaneously for patients weighing >40 kg will receive escalating doses to 4 mg/kg subcutaneously for patients weighing 15 to 40 kg or 300 mg subcutaneously for patients weighing >40 kg.

   The timetable you submitted on June 15, 2009, states that you will conduct this trial according to the following timetable:

Trial Completion Date:	by June 2010
Final Report Submission:	by September 2010

3. Complete and report the ongoing, multicenter, open-label, 6-month, clinical trial D2201 investigating the safety of higher doses of Ilaris (canakinumab). Patients in trial D2201 will receive a dose of 4 mg/kg subcutaneously for patients weighing less than 15 to 40 kg.

   The timetable you submitted on June 15, 2009, states that you will conduct this trial according to the following timetable:

Trial Completion Date:	by November 2010
Final Report Submission:	by January 2011

Submit the protocols to your IND 100040, with a cross-reference letter to this BLA 125319. Submit all final reports to your BLA 125319. Prominently identify submissions 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 NOT SUBJECT TO THE REPORTING REQUIREMENTS OF 21 CFR 601.70

We remind you of your postmarketing commitments described in your email dated June 15, 2009, and outlined below:

4. To provide an evaluation, summary, and data that confirm the adequacy of the proposed equilibration time required for thawed bulk drug substance to prevent excursions of drug product turbidity.

   Study Completion Date: by December 2009
   Final Report Submission: by February 2010

5. To perform validation studies on a (b) (4) for canakinumab drug substance. The protocol, final report, and the proposed specification will be submitted as a CBE-0 supplement.

   Study Completion Date: by October 2009
   Final Report Submission: by November 2009

6. To monitor canakinumab drug product for the appearance of new bands when compared to reference standard during the (b) (4) assessment of registration stability testing, and to set an appropriate (b) (4) specifications relative to reference

standard upon availability of 24 months of registration stability data for canakinumab drug product. The proposed specifications and stability data will be provided as a CBE-0 supplement.

Study Completion Date: by September 2010
Final Report Submission: by November 2010

7. To perform stability testing on at least one marketed drug product lot and one drug substance lot annually for each year in which drug substance and/or drug product is manufactured, using the post-approval stability protocol specified in the BLA. The first update will be included in an annual report.

Study Completion Date: by June 2010
Final Report Submission: by August 2010

8. To assess release and shelf-life specifications for canakinumab drug substance and drug product after manufacture of 15 lots. Specifications assessment and supporting data will be provided.

Study Completion Date: by June 2014
Final Report Submission: by August 2014

9. To qualify the additional biochemical characterization assays that will be used in support of establishing a new canakinumab reference standard. Qualification of currently used assays will be submitted.

Study Completion Date: by December 2009
Final Report Submission: by February 2010

ADVERSE EVENT REPORTING

You must submit adverse experience reports under the adverse experience reporting requirements for licensed biological products (21 CFR 600.80). We ask that you submit any adverse event reports related to malignancy, serious infections (including opportunistic infections and tuberculosis), serious hemorrhage, and serious skin reactions (e.g., Stevens Johnson Syndrome, toxic epidermal necrosis, and erythema multiforme) as 15-day reports, per reporting regulation 21 CFR 600.80. Serious events are defined as events leading to death, hospitalization, disability, or reported as life threatening. You should submit postmarketing adverse experience reports to the Central Document Room, Center for Drug Evaluation and Research, Food and Drug Administration, 5901-B Ammendale Road, Beltsville, MD 20705-1266. Prominently identify all adverse experience reports as described in 21 CFR 600.80.

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/ucm085692.htm.

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 the Division of Compliance Risk Management and Surveillance (HFD-330), Center for Drug Evaluation and Research, Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857. Biological product deviations sent by courier or overnight mail should be addressed to Food and Drug Administration, CDER, Office of Compliance, Division of Compliance Risk Management and Surveillance, 10903 New Hampshire Avenue, Bldg. 51, Room 4203, Silver Spring, MD 20993-0002.

CONTENT OF LABELING

Within 14 days of the date of this letter, submit content of labeling [21 CFR 601.14(b)] in structured product labeling (SPL) format, as described at http://www.fda.gov/oc/datacouncil/spl.html, that is identical in content to the enclosed labeling text. Upon receipt, we will transmit that version to the National Library of Medicine for public dissemination. For administrative purposes, designate this submission "**Product Correspondence – Final SPL for approved STN BLA 125319/0**."

We remind you that pursuant to 21 CFR 201.57(c)(18) and 201.80(f)(2), patient labeling must be reprinted immediately following the last section of labeling or, alternatively, accompany the prescription drug labeling. We request that the labeling approved today be available on your website within 10 days of receipt of this letter.

CARTON AND IMMEDIATE CONTAINER LABELS

Submit final printed carton and container labels that are identical to the enclosed draft 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 (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 "**Product Correspondence – Final Printed Carton and Container Labels for approved STN BLA 125319/0**." Approval of this submission by FDA is not required before the labeling is used.

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

PROMOTIONAL MATERIALS

You may submit draft copies of the proposed introductory advertising and promotional labeling with a cover letter requesting advisory comments to the Food and Drug Administration, Center for Drug Evaluation and Research, Division of Drug Marketing, Advertising and Communication, 5901-B Ammendale Road, Beltsville, MD 20705-1266. Final printed advertising and promotional labeling should be submitted at the time of initial dissemination, accompanied by a Form FDA 2253.

All promotional claims must be consistent with and not contrary to approved labeling. You should not make a comparative promotional claim or claim of superiority over other products unless you have substantial evidence to support that claim.

Please refer to http://www.fda.gov/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/TherapeuticBiologicApplications/default.htm for information regarding therapeutic biological products, including the addresses for submissions.

If you have any questions, contact Ramani Sista, Regulatory Project Manager, at 301-796-1236.

Sincerely,

Curtis J. Rosebraugh, M.D., M.P.H.
Director
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Enclosures:
Package Insert
Patient Package Insert
Carton and immediate container labels