DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 20-484/S-011

Celgene Corporation
Attention: Penny Ng, BSc, MBA, RAC
Senior Regulatory Specialist, Regulatory Affairs
9900 West 109th Street, Building 70, Suite 300
Overland Park, KS 66210

Dear Ms. Ng:

Please refer to your supplemental new drug application dated April 11, 2008, received April 14, 2008, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Innohep®, (tinzaparin sodium injection), 20,000 IU/mL.

We also refer to our November 14, 17, 19, and 24, and December 1, 2008, teleconferences.

We acknowledge receipt of your submissions dated November 14, 20, and 25, and December 2, 2008. Your submission of December 2, 2008 constituted a complete response to our October 14, 2008 action letter.

This supplemental application, submitted as "Supplement - Changes Being Effected" proposes the following change: Revision to the Package Insert to address an increased risk for death in elderly patients with renal insufficiency.

We completed our review of this application, as amended. This application is approved, effective on the date of this letter, for use as recommended in the agreed-upon labeling text.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, please submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format as described at http://www.fda.gov/oc/datacouncil/spl.html that is identical to the (package insert submitted December 02, 2008). Upon receipt, we will transmit that version to the National Library of Medicine for public dissemination. For administrative purposes, please designate this submission, "SPL for approved **NDA 20-484/S-011**."

In addition, the Division of Drug Marketing, Advertising, and Communications (DDMAC) has reviewed the revised product labeling and has determined that it contains significant new risk

information relating to your drug product. We are hereby requesting that all promotional materials for your drug product that include representations about your drug product be revised to include the new risk information immediately. These revisions should include prominent disclosure of the important new information described in the **CLINICAL PHARMACOLOGY**, **Special Populations**, **Elderly**, **WARNINGS**, **PRECAUTIONS, Geriatric Use**, and **ADVERSE REACTIONS** sections that appear in the revised package labeling. Please submit a written response to this request on or before 1 week of the date of this letter, stating whether you intend to comply with this request, to the Food and Drug Administration, Center for Drug Evaluation and Research, Division of Drug Marketing, Advertising, and Communications by facsimile at (301) 847-8444 or at 5901-B Ammendale Road, Beltsville, MD 20705-1266.

POSTMARKETING REQUIREMENTS UNDER 505(o)

Reference is made to the clinical trial sponsored by LEO Pharma, IN 0401 INT (IRIS), entitled "Safety Profile of Innohep® Versus Subcutaneous Unfractionated Heparin in Elderly Patients with Impaired Renal Function Treated for Acute Deep Vein Thrombosis" (the "IRIS" trial) and your submission of the preliminary data from this trial, as referenced above. Title IX, Subtitle A, Section 901 of the Food and Drug Administration Amendments Act of 2007 (FDAAA) amends the Federal Food, Drug, and Cosmetic Act (FDCA) to authorize 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), 21 U.S.C. 355(o)(3)(A)). This provision took effect on March 25, 2008.

Since Innohep® was approved in July 2000 for the treatment of acute symptomatic deep vein thrombosis with or without pulmonary embolism when administered in conjunction with warfarin sodium, we have become aware of postmarketing reports of deaths following Innohep® administration. Specifically, the "IRIS" trial indicated Innohep® therapy was associated with an increased risk for death among elderly patients with renal insufficiency, compared to the use of heparin therapy among these patients. This information was not available when Innohep® was granted marketing authorization. Therefore, we consider this information to be “new safety information” as defined in FDAAA.

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 the serious risk of death.

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 therefore not sufficient to assess these signals of a serious risk.

Finally, we have determined that only a clinical trial (rather than a nonclinical or observational study) will be sufficient to assess this signal of a serious risk.

Therefore, based on appropriate scientific data, FDA has determined that you are required, pursuant to section 505(o)(3) of the FDCA, to complete and submit a full report for the "IRIS" trial.

1. To complete and submit the final report, including electronic datasets, for the clinical trial entitled

   "Safety Profile of Innohep® Versus Subcutaneous Unfractionated Heparin in Elderly Patients with Impaired Renal Function Treated for Acute Deep Vein Thrombosis." Depending on the final results of the trial, you may be required to conduct another clinical trial to evaluate the risk of death with the use of Innohep.

   The timetable you submitted by e-mail on December 17, 2008, indicated that you will provide this report according to the following timetable:

   Final report submission: March, 2009

Submit the final report to your NDA 20-484. Use the following designators to prominently label all submissions, including supplements, relating to this postmarketing requirement 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 314.81(b)(2)(vii) 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 314.81(b)(2)(vii) 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 314.81(b)(2(vii). 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.

LETTERS TO HEALTH CARE PROFESSIONALS

Your submission of December 02, 2008 included a letter communicating important information about this drug product (i.e., a "Dear Health Care Professional" letter), we request that you submit a copy of the letter to the following address:

MEDWATCH
Food and Drug Administration
Suite 12B05
5600 Fishers Lane
Rockville, MD 20857

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 questions, contact Marcus Cato, Regulatory Project Manager, at (301) 796-3903.

Sincerely,

{See appended electronic signature page}

Rafel (Dwaine) Rieves, MD
Division Director
Division of Medical Imaging and Hematology Products
Office of Oncology Drug Products
Center for Drug Evaluation and Research

Enclosure: Package Insert

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

/s/

Rafel Rieves

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