DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 20718/S-034

SUPPLEMENT APPROVAL

Schering-Plough
Attention: Deborah Urquhart, Ph.D.
Director and Liaison, Global Regulatory Affairs
2000 Galloping Hill Road
Kenilworth, NJ 07033

Dear Dr. Urquhart:

Please refer to your Supplemental New Drug Application (sNDA) dated August 27, 2010, received, submitted under section 505(b)/ of the Federal Food, Drug, and Cosmetic Act (FDCA) for Integrilin (eptifibatide) 0.75 and 2 mg/mL Injection.

We acknowledge receipt of your amendments dated February 4 and March 18, 2011.

This supplemental new drug application provides for the following revisions to the package insert:

1. Under **WARNINGS, Renal Insufficiency,** the last sentence was modified so that the section now reads:

   Renal Insufficiency
   Approximately 50% of eptifibatide is cleared by the kidney in patients with normal renal function. Total drug clearance is decreased by approximately 50% and steady-state plasma eptifibatide concentrations are doubled in patients with an estimated creatinine clearance <50 mL/min (using the Cockcroft-Gault equation). Therefore, the infusion dose should be reduced to 1 mcg/kg/min in such patients (see **DOSAGE AND ADMINISTRATION**). The safety and efficacy of eptifibatide in patients dependent on dialysis has not been established.

2. Under **PRECAUTIONS**, references to Thrombocytopenia have been deleted and moved to **WARNINGS**. The **WARNINGS /Thrombocytopenia** section now reads as follows:

   Thrombocytopenia
   In the event of acute profound thrombocytopenia or a confirmed platelet decrease to <100,000mm^3, discontinue Integrilin and heparin (unfractionated or low-molecular-weight). Monitor serial platelet counts, assess the presence of drug-dependent antibodies, and treat as appropriate (see **ADVERSE REACTIONS, Immunogenicity**).

There has been no clinical experience with eptifibatide initiated in patients with a baseline platelet count <100,000mm^3**. If a patient with low platelet counts is receiving Integrilin, their platelet count should be monitored closely.**

3. Under **ADVERSE REACTIONS, Allergic Reactions**, a new section entitled "Immunogenicity" was added. This section appears as follows:

   Immunogenicity
   The potential for development of antibodies to eptifibatide was studied in 433 subjects. Eptifibatide was nonantigenic in 412 patients receiving a single administration of eptifibatide (135-µg/kg bolus followed by a continuous infusion of either 0.5 µg/kg/min or 0.75 µg/kg/min), and in 21 subjects to whom eptifibatide (135-µg/kg bolus followed by a continuous infusion of 0.75 µg/kg/min) was administered twice, 28 days apart. In both cases, plasma for antibody detection was collected approximately 30 days after each dose. The development of antibodies to eptifibatide at higher doses has not been evaluated.

   Post-marketing, there have been reports of immune-mediated thrombocytopenia with eptifibatide. IgG antibodies that react with the glycoprotein IIb/IIIa complex were identified in the presence of eptifibatide and in eptifibatide naïve patients. These findings suggest acute thrombocytopenia after the administration of eptifibatide can develop as a result of naturally occurring drug-dependent antibodies or those induced by prior exposure to eptifibatide. Similar antibodies were identified with other GP IIb/IIIa ligand-mimetic agents. Immune-mediated thrombocytopenia with eptifibatide may be associated with hypotension and/or other signs of hypersensitivity.

4. Under **ADVERSE REACTIONS, Post-Marketing**, the event, "immune mediated thrombocytopenia" was added with a cross reference to **ADVERSE REACTIONS, Immunogenicity** section.

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 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 http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm. Content of labeling must be identical to the enclosed labeling (text for the package insert, text for the patient package insert, Medication Guide), 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 titled "SPL Standard for Content of Labeling Technical Qs and As" at http://www.fda.gov/downloads/DrugsGuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf.

The SPL will be accessible from publicly available labeling repositories.

Also within 14 days, amend all pending supplemental applications 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 MS Word format, that includes the changes approved in this supplemental application, as well as annual reportable changes and annotate each change. To facilitate review of your submission, 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).

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 package insert(s) to:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Drug Marketing, Advertising, and Communications
5901-B Ammendale Road
Beltsville, MD 20705-1266

You must submit final promotional materials and package insert(s), 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 http://www.fda.gov/opacom/morechoices/fdaforms/cder.html; instructions are provided on page 2 of the form. For more information about submission of promotional materials to the Division of Drug Marketing, Advertising, and Communications (DDMAC), see 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 package 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 or by fax to 301-847-8444.

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, please call:

Alison Blaus
Regulatory Project Manager
(301) 796 - 1138

Sincerely,

{See appended electronic signature page}

Mary Ross Southworth, Pharm.D.
Deputy Director for Safety
Division of Cardiovascular and Renal Products
Office of Drug Evaluation I
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/

MARY R SOUTHWORTH
03/30/2011