DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 021938/S-028
NDA 021938/S-029

SUPPLEMENT APPROVAL

C.P. Pharmaceuticals International
Attention: Brian F. Caselli, MSc
445 Eastern Point Rd.
MS-8260-1118
Groton, CT 06340

Dear Mr. Caselli:

Please refer to your Supplemental New Drug Applications (sNDAz) for Supplement-028 and Supplement-029 dated September 25, 2014, and October 24, 2014, respectively, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Sutent® (sunitinib malate) Capsules.

We also refer to our Supplement Request letter dated September 9, 2014, notifying you, under Section 505(o)(4) of the FDCA, of new safety information that we believe should be included in the labeling for Sutent® (sunitinib malate). This information pertains to the risk of thrombotic microangiopathy, hemolytic uremic syndrome, and thrombocytopenic purpura along with the risk of renal failure and death.

The Prior Approval supplemental new drug application, for Supplement-028, provides for the following changes:

1. Revised wording under HIGHLIGHTS, WARNINGS AND PRECAUTION section, "Cardio Toxicity" changed to "Cardiovascular events including myocardial ischemia, myocardial infarction."
2. Revised wording under FULL PRESCRIBING INFORMATION, WARNINGS AND PRECAUTIONS section 5.3 for the following:
    a. "Left Ventricular Dysfunction" changed to "Cardiovascular Events."
    b. "Myocardial disorders" changed to "myocardial ischemia, myocardial infarctions."
    c. Addition of sentence, "Use SUTENT with caution in patients who are at risk for, or who have a history of these events."
3. Revised wording under FULL PRESCRIBING INFORMATION, OVERDOSEAGE section 10: "A few cases of accidental overdose" changed to "Cases of accidental overdose."
4. Added "Heart attack" as a possible side effect to the Medication Guide.

The Prior Approval supplemental new drug application, Supplement-029, provides for the following changes:

1. The HIGHLIGHTs, WARNINGS AND PRECAUTIONS and FULL PRESCRIBING INFORMATION, WARNINGS AND PRECAUTIONS sections were both re-numbered. Warnings with fatal outcomes were elevated to align the label with the Guidance for Industry: "Warning and Precautions, Contraindications, and Boxed Warning Sections of Labeling for Human Prescription Drug and Biological Products – Content and Format."
2. Additional warning added to HIGHLIGHTS section under WARNINGS AND PRECAUTIONS, "Thrombotic Microangiopathy, thrombotic thrombocytopenic purpura and hemolytic uraemic syndrome sometimes leading to renal failure or fatal outcome, has been reported in clinical trials and in post-marketing experience of Sutent."
3. The above warning also added to FULL PRESCRIBING INFORMATION, WARNINGS AND PRECAUTIONS, section 5.11 and PATIENT COUNSELING INFORMATION section 17.6. Subsequent sections re-numbered accordingly.
    a. FULL PRESCRIBING INFORMATION, WARNINGS AND PRECAUTIONS, section 5.11, language reads as follows: "Thrombotic microangiopathy (TMA), including thrombotic thrombocytopenic purpura and hemolytic uremic syndrome, sometimes leading to renal failure or a fatal outcome, has been reported in clinical trials and in post-marketing experience of SUTENT as monotherapy and in combination with bevacizumab. Discontinue SUTENT in patients developing TMA. Reversal of the effects of TMA has been observed after treatment was discontinued."
    b. PATIENT COUNSELING INFORMATION section reads: "Thrombotic microangiopathy leading to renal insufficiency and neurologic abnormalities was observed in patients who received SUTENT as a monotherapy or in combination with bevacizumab. Patients should be advised that signs and symptoms of thrombotic microangiopathy may occur during treatment with SUTENT. Patients should be advised to immediately inform their healthcare provider if signs and symptoms of thrombotic microangiopathy occur."
4. Proteinuria added to PATIENT COUNSELING INFORMATION section and reads as follows: "Proteinuria and nephrotic syndrome has been reported. Patients should be advised that urinalysis will be performed prior to starting as well as during treatment with SUTENT. In cases with impact to renal function, treatment with SUTENT may be interrupted or discontinued."
5. Thrombotic Microangiopathy removed from Post-marketing Experience Section.
6. The following information was added under possible side effect to the Medication Guide: "**Damage to the smallest blood vessels**. Damage to the smallest blood vessels known as thrombotic microangiopathy (TMA) may occur. TMA is a condition involving injury to the vessels and resulting blood clots and is accompanied by injury to red blood cells leading to a decrease in red cells and a decrease in cells that are involved with clotting. TMA may harm organs such as the brain and kidneys. Symptoms of TMA may include fever, fatigue, tiredness, bruising; you may develop swelling, confusion, vision loss, and seizures. Your healthcare provider may tell you to stop taking SUTENT."

APPROVAL & LABELING

We have completed our review of these supplemental applications. They are 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 and 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 that includes labeling changes 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
Office of Prescription Drug Promotion (OPDP)
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/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.

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, call Jeannette O'Donnell, Regulatory Project Manager, at (240) 402-4978 or email: Jeannette.Odonnell@fda.hhs.gov.

Sincerely,

{See appended electronic signature page}

Geoffrey Kim, MD
Director
Division of Oncology Products 1
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

ENCLOSURE(S):
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/

GEOFFREY S KIM
04/24/2015