DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 203585

ACCELERATED APPROVAL

IVAX International GmbH
Attention: Carol Marchione, Authorized U.S. Agent
Head of Global Oncology Regulatory Affairs
Teva Branded Pharmaceuticals Products R&D, Inc.
41 Moores Road
P.O. Box 4011
Frazer, PA 19355

Dear Ms. Marchione:

Please refer to your New Drug Application (NDA) dated March 30, 2012, received March 30, 2012, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Synribo (omacetaxine mepesuccinate) lyophilized powder for injection, 3.5 mg/vial.

We acknowledge receipt of your amendments dated April 5, 9, 24 (2), 26; May 8 (2), 11 (3), 21; June 4, 13, 20, 21, 28; July 2, 9, 12, 17, 24, 27; August 10, 14, 21, 22, 31; September 6, 14, 17; October 1, 16, and 25, 2012.

This new drug application provides for the use of Synribo (omacetaxine mepesuccinate) lyophilized powder for injection, 3.5 mg/vial for the treatment of adult patients with chronic or accelerated phase chronic myeloid leukemia (CML) with resistance and/or intolerance to two or more tyrosine kinase inhibitors (TKI).

We have completed our review of this application, as amended. It is approved under the provisions of accelerated approval regulations (21 CFR 314.500), effective on the date of this letter, for use as recommended in the enclosed agreed-upon labeling text. Marketing of this drug product and related activities must adhere to the substance and procedures of the referenced accelerated approval regulations.

Based on the provided stability data, an 18-month expiration dating period is granted for the drug product, when stored at 20°C to 25°C (68°F to 77°F), excursions permitted to 15°C to 30°C; and protected from light.

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). 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.

CARTON AND IMMEDIATE CONTAINER LABELS

Submit final printed carton and container labels that are identical to the enclosed carton and immediate container labels, and those carton and immediate container labels submitted on October 25, 2012, 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 (June 2008)." 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 "**Final Printed Carton and Container Labels for approved NDA 203585**." Approval of this submission by FDA is not required before the labeling is used.

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

Please submit one market package of the drug product when it is available to the following address:

Theresa Ferrara Carioti, Regulatory Project Manager
Food and Drug Administration
Center for Drug Evaluation and Research
White Oak Building 22, Room: 2317
10903 New Hampshire Avenue
Silver Spring, Maryland
Use zip code **20903** *if shipping via United States Postal Service (USPS).*
Use zip code **20993** *if sending via any carrier other than USPS (e.g., UPS, DHL, FedEx).*

ADVISORY COMMITTEE

Your application for Synribo (omacetaxine mepesuccinate) was not referred to an FDA advisory committee because it was discussed at a previous advisory committee meeting on March 22, 2010 under NDA 22374, and a complete response letter was issued April 8, 2010 for NDA 22374.

ACCELERATED APPROVAL REQUIREMENTS

Products approved under the accelerated approval regulations, 21 CFR 314.510, require further adequate and well-controlled studies/clinical trials to verify and describe clinical benefit. You are required to conduct such studies/trials with due diligence. If postmarketing studies/trials fail to verify clinical benefit or are not conducted with due diligence, we may, following a hearing in accordance with 21 CFR 314.530, withdraw this approval. We remind you of your postmarketing requirement specified in your submission dated October 1, 2012. This requirement, along with required completion dates, is listed below.

1930-1 Continue follow-up of patients (on treatment and in protocol defined post-treatment follow-up) and submit a final analysis report of CGX-635-CML-300 with 24 months of minimum follow-up data for each patient. If 24 months of follow-up is not possible for certain patients, justification should be provided.

Preliminary Protocol Submission:	N/A
Final Protocol Submission:	N/A
24 Month Follow-up Completion:	03/2012
Final Report Submission:	04/2013

Submit final reports to this NDA as a supplemental application. For administrative purposes, all submissions relating to this postmarketing requirement must be clearly designated "**Subpart H Postmarketing Requirement(s)**."

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 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.

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 increased exposure to Synribo (omacetaxine mepesuccinate) and related toxicity secondary to organ impairment and the need to optimize the dosing regimen.

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.

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 of increased exposure to Synribo (omacetaxine mepesuccinate) and related toxicity secondary to organ impairment and the need to optimize the dosing regimen.

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

1930-2 Conduct a Phase 1/2 single arm clinical trial to investigate the pharmacokinetic, safety, and preliminary efficacy of omacetaxine following fixed dose administration in patients with chronic phase (CP) or accelerated phase (AP) chronic myeloid leukemia (CML) who have failed two or more TKI therapies.

In Cycle 1 evaluate the PK and safety of omacetaxine following a fixed dose administration. Continue treatment, if tolerated, using a fixed dose as long as patients are clinically benefiting from therapy.

The timetable you submitted on October 1, 2012, states that you will conduct this trial according to the following schedule:

Preliminary Protocol Submission:	12/2012
*Final Protocol Submission:	03/2013
Trial Completion:	02/2016
Final Report:	06/2016

*Note that the "Final Protocol Submission" date is the date on which you submit a complete protocol that has already received full concurrence by FDA.

1930-3 Conduct a mass balance trial in humans to determine the disposition and elimination pathways as well as to characterize the major metabolites of omacetaxine following subcutaneous injection. Depending on the results, hepatic and/or renal impairment trials may be required.

The timetable you submitted on October 1, 2012, states that you will conduct this trial according to the following schedule:

Preliminary Protocol Submission:	07/2012
*Final Protocol Submission:	10/2012
PK Report:	06/2015
Trial Completion:	07/2015
Final Report	12/2015

*Note that the "Final Protocol Submission" date is the date on which you submit a complete protocol that has already received full concurrence by FDA.

Submit the protocol(s) to your IND 62384, with a cross-reference letter to this NDA. Submit all final report(s) to your NDA. 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 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.

PROMOTIONAL MATERIALS

Under 21 CFR 314.550, you are required to submit, during the application pre-approval review period, all promotional materials, including promotional labeling and advertisements, that you intend to use in the first 120 days following marketing approval (i.e., your launch campaign). If you have not already met this requirement, you must immediately contact the Office of Prescription Drug Promotion (OPDP) at (301) 796-1200. Please ask to speak to a regulatory project manager or the appropriate reviewer to discuss this issue.

As further required by 21 CFR 314.550, submit all promotional materials that you intend to use after the 120 days following marketing approval (i.e., your post-launch materials) at least 30 days before the intended time of initial dissemination of labeling or initial publication of the advertisement. We ask that each submission include a detailed cover letter together with three copies each of the promotional materials, annotated references, and approved package insert (PI)/Medication Guide/patient PI (as applicable).

Send each submission directly to:

OPDP Regulatory Project Manager
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Prescription Drug Promotions (OPDP)
5901-B Ammendale Road
Beltsville, MD 20705-1266

REPORTING REQUIREMENTS

We remind you that you must comply with the reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

MEDWATCH-TO-MANUFACTURER PROGRAM

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/ucm166910.htm.

POST-ACTION FEEDBACK MEETING

New molecular entities and new biologics qualify for a post-action feedback meeting. Such meetings are used to discuss the quality of the application and to evaluate the communication process during drug development and marketing application review. The purpose is to learn from successful aspects of the review process and to identify areas that could benefit from improvement. If you would like to have such a meeting with us, call the Regulatory Project Manager for this application.

If you have any questions, call Theresa Ferrara Carioti, Regulatory Project Manager, at (301) 796-2848.

Sincerely,

{See appended electronic signature page}

Richard Pazdur, MD
Director
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

ENCLOSURES:
Content of Labeling
Carton and Container Labeling

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

/s/

RICHARD PAZDUR
10/26/2012