ZyPharma

ZYDUS PHARMACEUTICALS

A GLOBAL GENERIC PHARMACEUTICAL COMPANY

ZyGenerics

August 13, 2013

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To,

Division of Dockets Management
Food and Drug Administration (HFA-305)
Department of Health and Human Services
5630 Fishers Lane, Room 1061
Rockville, Maryland 20852

SUITABILITY PETITION

Dear Sir or Madam,

This petition is submitted in quadruplicate pursuant to Section 505(j)(2)(C) of the Federal Food, Drug, and Cosmetic Act ("FDC Act"), and 21 C.F.R. 314.93, and in accordance with 21 C.F.R. § 10.20 and 21 C.F.R. § 10.30, to request that the Food and Drug Administration ("FDA) determine that Imatinib Mesylate Tablets in strength of 300 mg is suitable for submission in an Abbreviated New Drug Application ("ANDA").

A. Action Requested

The petitioner requests that Commissioner of the Food and Drug Administration make a determination that Imatinib Mesylate Tablets, 300 mg is suitable for submission in an ANDA. This petition is based on the Reference Listed Drug ("RLD") GLEEVEC (Imatinib Mesylate) Tablets 100 mg and 400 mg, approved on April 18, 2003 under NDA No. 021588 held by Novartis Pharmaceuticals Corporation ("Novartis") and a Citizen Petition filed by Hyman, Phelps & McNamara, P.C. dated June 25, 2010 seeking suitability to submit three new tablet strengths - 50 mg, 200 mg, and 600 mg - was approved by FDA on November 15, 2012. Therefore, the petitioner seeks a 300 mg strength which is between the highest and lowest strengths approved for the RLD (100 mg and 400 mg).

B. Statement of Grounds

The Federal Food, Drug and Cosmetics Act 505(j)(2)(A) permits the submission of an ANDA for a new drug that differs in strength from the listed drug after FDA has approved a petition submitted pursuant to FDC Act § 505(j)(2)(C). The RLD for the proposed drug product, GLEEVEC (Imatinib Mesylate) Tablets, contains either 100 mg or 400 mg of Imatinib Mesylate. The RLD is identified in the current edition of the Electronic Orange book (**see Attachment I**). Additionally, a Suitability Petition filed by Hyman, Phelps & McNamara, P.C. dated June 25, 2010 seeking suitability to submit three new tablet strengths - 50 mg, 200 mg, and 600 mg - was

Zydus Pharmaceuticals (USA) Inc.
73, Route 31 North • Pennington, NJ 08534
Ph. 609-730-1900 • Fax 609-730-1999 • www.zydususa.com

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approved by FDA on November 15, 2012. **(see Attachment II).** Imatinib Mesylate is a protein-tyrosine kinase inhibitor that inhibits the bcr-abl tyrosine kinase, the constitutive abnormal tyrosine kinase created by the Philadelphia chromosome abnormality that is approved for several indications. The proposed drug product represents the same dosage form and route of administration and represents intermediate dosage strength relative to the high and low doses approved for the RLD. The following table compares the two drug products.

Product Name	Dosage form	Route of administration	Strengths
RLD: GLEEVEC (Imatinib Mesylate)	Tablet	Oral	100 mg and 400 mg
Imatinib Mesylate by Hyman, Phelps & McNamara, P.C, for additional strengths	Tablet	Oral	50 mg, 200 mg and 600 mg
Proposed Imatinib Mesylate	Tablet	Oral	300 mg

Petitioner's proposed drug product in the new 300 mg strength does not pose questions of safety or efficacy. The uses, dosage form, and route of administration are the same as those of the RLD. The only difference between the proposed product and the RLD is the strength. The dosing instructions for the RLD are as follows:

- Adults with Ph+ CML CP (2.1): 400 mg/day
- Adults with Ph+ CML AP or BC (2.1): 600 mg/day
- Pediatrics with Ph+ CML (2.2): 340 mg/m^2/day or 260 mg/m^2/day
- Adults with Ph+ ALL (2.3): 600 mg/day
- Adults with MDS/MPD (2.4): 400 mg/day
- Adults with ASM (2.5): 100 mg/day or 400 mg/day
- Adults with HES/CEL (2.6): 100 mg/day or 400 mg/day
- Adults with DFSP (2.7): 800 mg/day
- Adults with GIST (2.8): 400 mg/day
- Patients with mild to moderate hepatic impairment (2.9): 400 mg/day
- Patients with severe hepatic impairment (2.9): 300 mg/day

All doses of Gleevec should be taken with a meal and a large glass of water. Doses of 400 mg or 600 mg should be administered once daily, whereas a dose of 800 mg should be administered as 400 mg twice a day. Gleevec can be dissolved in water or apple juice for patients having difficulty swallowing. Daily dosing of 800 mg and above should be accomplished using the 400 mg tablet to reduce exposure to iron.

Thus, the RLD labeling provides for a recommended dose of 300mg/day for patients in following condition (refer **attachment-III**):

1. Dose of 300 mg/day to be taken by patients with severe hepatic impairment.

2. In case of hepatotoxicity and non-hematologic reactions indicates that "If elevations in bilirubin >3 x institutional upper limit of normal (IULN) or in liver transaminases >5 x IULN occur, GLEEVEC should be withheld until bilirubin levels have returned to a <1.5 x IULN and transaminase levels to <2.5 x IULN. In adults, treatment with GLEEVEC may then be continued at a reduced daily dose (i.e., **400 mg to 300 mg**, 600 mg to 400 mg or 800 mg to 600 mg). In children, daily doses can be reduced under the same circumstances from 340 mg/m^2/day to 260 mg/m^2/day.

3. For neutropenia and thrombocytopenia indicates dose reduction of GLEEVEC to 300 mg/day as mentioned below:

Chronic Phase CML (starting dose 400 mg) MDS/MPD, ASM and HES/CEL (starting dose 400 mg) GIST (starting dose 400 mg)	ANC <1.0 x 109/L and/or platelets <50 x 109/L	Stop Gleevec until ANC ≥1.5 x 109/L and platelets ≥75 x 109/L Resume treatment with Gleevec at the original starting dose of 400 mg If recurrence of ANC <1.0 x 109/L and/or platelets <50 x 109/L, repeat step 1 and resume Gleevec at a **reduced dose of 300 mg**
Ph+ CML : Accelerated Phase and Blast Crisis (starting dose 600 mg) Ph+ ALL (starting dose 600 mg)	ANC <0.5 x 109/L and/or platelets <10 x 109/L	Check if cytopenia is related to leukemia (marrow aspirate or biopsy) If cytopenia is unrelated to leukemia, reduce dose of Gleevec to 400 mg If cytopenia persists 2 weeks, reduce further to **300 mg** If cytopenia persists 4 weeks and is still unrelated to leukemia, stop Gleevec until ANC ≥1 x 109/L and platelets ≥20 x 109/L and **then resume treatment at 300 mg**

Based on Office of Generic Drugs (OGD) recommendation in response to the controlled correspondence (Control # 13-0278) to FDA dated on April 17, 2013 regarding tablet scoring guidance, FDA recommendations were ***"Both of your proposed upper strengths, the 200 mg and 600 mg strengths, be scored. As such, the split 600 mg portion would provide a 300 mg dose and a split 200 tablet would provide a 100 mg dose therefore allowing a combination of whole and split units to cover the entire dosing regimen".***

Hence with the approval of a 300 mg tablet strength, patients can administer a whole tablet instead of a split tablet (i.e., with 600 mg tablet) which facilitates improved patient compliance and accuracy of dosing.

The 300 mg strength would potentially improve patient compliance and provide a greater selection of tablet strengths to make it easier to meet the dosing recommendations. For example, a patient could take a single 300 mg tablet instead of half of a 600 mg tablet or three 100 mg tablets or one 200 mg and one 100 mg tablets. The availability of this additional strength will also provide prescribing physicians with a greater degree of flexibility in selecting proper individualized maintenance doses for a specific patient's need within the current dosing instructions for the RLD.

The proposed Imatinib Mesylate Tablets drug product in a 300 mg tablet strength is intended for use only as described in the "Indications and Usage" and "Dosage and Administration" RLD labeling sections. The labeling for the proposed drug product would only differ from the RLD labeling only with respect to identification of the drug product strength and manufacturer-specific information. Draft labeling for the proposed Imatinib Mesylate Tablets drug product is provided in **Attachment IV.**

Obviously, there is no safety or efficacy concerns regarding administration of 300 mg strength as proposed by Zydus as its use, dose, dosage form, and route of administration are the same as that of the reference-listed drug product.

Inapplicability of the Pediatric Research Equity Act ("PREA '7). PREA, which is codified at FDC Act § 505B, does not apply to a new strength, such as the ones proposed in this Petition. See FDC Act § 505B(a)(l)(A). As such, PREA should not serve as an impediment to FDA granting this Petition.

For the foregoing reasons, Petitioner requests that FDA find that Imatinib Mesylate Tablets, 300 mg, is suitable for submission in an ANDA.

C. Environmental Impact

The environmental impact report on the action requested in this petition is not required under 21 CFR §25.31.

D. Economic Impact Statement

Pursuant to 2 1 CFR § 10.30(b), economic impact information to this petition is to be submitted only when requested by the Commissioner. If requested, the economic impact statement will be submitted.

E. Certification

The undersigned certifies that, to the best knowledge and belief of the undersigned, this petition includes all information and views on which the petition relies, and that it includes representative data and information known to the petitioner, which is unfavorable to the petition.

Sincerely,

G. Srinivas
Head of Regulatory Affairs
Zydus Pharmaceuticals (USA) Inc.

From: (609) 730-1900
Zydus Pharmaceuticals USA Inc
Zydus Pharmaceuticals USA Inc
73 Route 31 North

Pennington, NJ 08534

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Division of Docket Management
FDA (HFA-305)
5630 Fishers Lane,
Room 1061
ROCKVILLE, MD 20852

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