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## Inspections, Compliance, Enforcement, and Criminal Investigations

### Novartis Oncology 4/21/10



Department of Health and Human Services

Public Health Service  
Food and Drug Administration  
Silver Spring, MD 20993

#### TRANSMITTED BY FACSIMILE

Ludwig Hantson, Ph.D.  
CEO  
Novartis Pharmaceuticals Corporation  
One Health Plaza  
East Hanover, NJ 07936-1080

#### RE: NDA 021588

Gleevec® (imatinib mesylate)  
MACMIS # 18492

#### WARNING LETTER

Dear Dr. Hantson:

As part of its monitoring and surveillance program, the Division of Drug Marketing, Advertising, and Communications (DDMAC) of the U.S. Food and Drug Administration (FDA) has reviewed two websites ([www.gistalliance.com](http://www.gistalliance.com) and [www.cmlalliance.com](http://www.cmlalliance.com)) sponsored by Novartis. As explained more fully below, these websites represent branded promotional material for Gleevec® (imatinib mesylate) (Gleevec). These websites are false and misleading because they promote the drug for an unapproved use, fail to disclose the risks associated with the use of Gleevec and make unsubstantiated dosing claims.<sup>1</sup> Therefore, these websites misbrand the drug in violation of the Federal Food, Drug, and Cosmetic Act (the Act), 21 U.S.C. 352(a), (f)(1) & (n); 321(n), and FDA implementing regulations. See 21 CFR 201.100(c), 201.115 & 201.128, 21 CFR 202.1(e)(5), (e)(6)(i), (iv) & (xi). Furthermore, it appears that these materials were neither submitted to FDA 30 days prior to the intended time of initial dissemination or initial publication as required by 21 CFR 314.550, nor submitted to FDA on Form FDA 2253 at the time of initial dissemination or initial publication, as required by 21 CFR 314.81(b)(3)(i).

These websites are concerning from a public health perspective because they promote Gleevec for an unapproved use, fail to disclose the risks associated with the use of Gleevec, and make unsubstantiated dosing claims about this medication that can put patients at higher risk of experiencing serious adverse events.

#### Background

According to the FDA-approved product labeling (PI), Gleevec is indicated, among other things, for:

- Newly diagnosed adult patients with Philadelphia chromosome positive chronic myeloid leukemia [Ph+ CML] in the chronic phase
- Patients with Philadelphia chromosome positive chronic myeloid leukemia in blast crisis, accelerate phase, or in chronic phase after failure of interferon-alpha therapy
- Patients with Kit (CD117) positive unresectable and/or metastatic malignant gastrointestinal stromal tumors [GIST]
- Adjuvant treatment of adult patients following complete gross resection of Kit (CD117) positive GIST

Gleevec's original approval on April 18, 2003, was an accelerated approval under 21 CFR 314 subpart H, and some of its indicated uses (e.g. adjuvant GIST) remain under the accelerated approval regulations.

Gleevec is associated with a number of Warnings and Precautions. For example:

- Edema and severe fluid retention have occurred. Weigh patients regularly and manage unexpected rapid weight gain by drug interruption and diuretics.
- Cytopenias, particularly anemia, neutropenia, and thrombocytopenia, have occurred. Manage with dose reduction or dose interruption and in rare cases discontinuation of treatment. Perform complete blood counts weekly for the first month, biweekly for the second month, and periodically thereafter.
- Severe congestive heart failure and left ventricular dysfunction have been reported, particularly in patients with comorbidities and risk factors. Patients with cardiac disease or risk factors for cardiac failure should be monitored and treated.
- Severe hepatotoxicity may occur. Assess liver function before initiation of treatment and monthly thereafter or as clinically indicated. Monitor liver function when combined with chemotherapy known to be associated with liver dysfunction.
- Grade 3/4 hemorrhage has been reported in clinical studies in patients with newly diagnosed CML and with GIST. GI tumor sites may be the source of GI bleeds in GIST.
- Gastrointestinal perforations, some fatal, have been reported.
- Bullous dermatologic reactions (e.g., erythema multiforme and Stevens-Johnson syndrome) have been reported with the use of Gleevec.
- Hypothyroidism has been reported in thyroidectomy patients undergoing levothyroxine replacement. Closely monitor TSH levels in such patients.
- Consider potential toxicities, specifically, liver, kidney, and cardiac toxicity, and immunosuppression from long-term use.
- Fetal harm can occur when administered to a pregnant woman. Women should be apprised of the potential harm to the fetus.

The PI also states that the most frequently reported adverse reactions (across indications) (>30%) were edema, nausea, vomiting, muscle cramps, musculoskeletal pain, diarrhea, rash, fatigue and abdominal pain.

The DOSAGE AND ADMINISTRATION section states (in pertinent part):

Treatment may be continued as long as there is no evidence of progressive disease or unacceptable toxicity.

#### ....Adult Patients with Ph+ CML CP, AP and BC

The recommended dose of Gleevec is 400 mg/day for adult patients in chronic phase CML and 600 mg/day for adult patients in accelerated phase or blast crisis. In CML, a dose increase from 400 mg to 600 mg in adult patients with chronic phase disease, or from 600 mg to 800 mg (given as 400 mg twice daily) in adult patients in accelerated phase or blast crisis may be considered in the absence of severe adverse drug reaction and severe non-leukemia related neutropenia or thrombocytopenia in the following circumstances: disease progression (at any time), failure to achieve a satisfactory hematologic response after at least 3 months of treatment, failure to achieve a cytogenetic response after 6-12 months of treatment, or loss of a previously achieved hematologic or cytogenetic response.

#### ....GIST

The recommended dose of Gleevec is 400 mg/day for adult patients with unresectable and/or metastatic malignant GIST. A dose increase up to 800 mg daily (given as 400 mg twice daily) may be considered, as clinically indicated, in patients showing clear signs or symptoms of disease progression at a lower dose and in the absence of severe adverse drug reactions.

The recommended dose of Gleevec is 400 mg/day for the adjuvant treatment of adult patients following complete gross resection of GIST. In the clinical study, Gleevec was administered for one year. The optimal treatment duration with Gleevec is not known.

The DOSAGE AND ADMINISTRATION section of the Gleevec PI also contains important dose modification guidelines for patients with hepatic or renal impairment.

The likelihood of developing an adverse reaction to Gleevec increases with higher doses. In the event of certain severe adverse reactions, such as hepatotoxicity, cytopenias, or severe fluid retention, the DOSAGE AND ADMINISTRATION section of the Gleevec PI includes the following detailed instructions for dose reduction or discontinuation (in pertinent part):

*Dose Adjustment for Hepatotoxicity and Non-Hematologic Adverse Reactions:* 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).... If a severe non-hematologic adverse reaction develops (such as severe hepatotoxicity or severe fluid retention), Gleevec should be withheld until the event has resolved. Thereafter, treatment can be resumed as appropriate depending on the initial severity of the event.

Dose Adjustment for Hematologic Adverse Reactions: Dose reduction or treatment interruptions for severe neutropenia and thrombocytopenia [in chronic phase CML and GIST] are recommended as [follows]:

Chronic Phase	ANC $<1.0 \times 10^9/L$	1. Stop Gleevec until ANC $\geq 1.5 \times 10^9/L$ and platelets $\geq 75 \times 10^9/L$
CML (starting dose 400 mg)	and/or	2. Resume treatment with Gleevec at the original starting dose of 400 mg
GIST (starting dose 400 mg)	platelets $<50 \times 10^9/L$	3. If recurrence of ANC $<1.0 \times 10^9/L$ and/or platelets $<50 \times 10^9/L$ , repeat step 1 and resume Gleevec at a reduced dose of 300 mg

## Misleading Product Claim Websites

While not using the established name of the Novartis drug product - Gleevec - the two Novartis-sponsored websites, [www.gistalliance.com](http://www.gistalliance.com) and [www.cmlalliance.com](http://www.cmlalliance.com), effectively promote this drug product for the treatment of GIST tumors and CML, respectively.

Specifically:

- The websites discuss the use of tyrosine kinase inhibitors (TKIs) for the first line treatment of GIST and CML, often in conjunction with the Novartis name. Gleevec is the only tyrosine kinase inhibitor (TKI) indicated for first-line treatment of chronic phase CML; the only TKI indicated for first line treatment of GIST; and the only TKI made by Novartis that is indicated for both GIST and CML. These product details are wellknown in the oncology community.
- The websites contain numerous references to the National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines in Oncology, which recommend the use of Gleevec exclusively for the first-line treatment of CML and GIST.
- The websites are perceptually similar to the Novartis Gleevec product website, incorporating similar color schemes (including a distinct orange), design layouts and other presentation elements.
- The websites are clearly marked with the Novartis Oncology name and logo and/or the Novartis name and logo and discuss sponsorship by Novartis Pharmaceuticals Corporation.
- The healthcare professional-directed "Targeting BCR-ABL" webpage on the CML Alliance website provides a direct link to the Novartis Gleevec product website in reference to first-line therapy for CML, while the consumer-directed version of this page provides a link to the Novartis-sponsored "My CML Circle Program" website, which discusses Gleevec as a treatment for CML.<sup>2</sup>
- The websites are registered to Novartis AG.<sup>3</sup>
- The websites present data from imatinib clinical studies, and provide the corresponding literature references, which include the drug name in the listed publication titles. At least one of the publications<sup>4</sup> recounts the pivotal clinical trial submitted to FDA in support of the approval of Gleevec in the treatment of adjuvant GIST.

Based on this combination of factors, these websites are product specific promotions for the drug Gleevec. Consequently, these websites are subject to regulation by FDA, and are false or misleading for the reasons described below.

## Promotion of Unapproved Use

The website [www.gistalliance.com](http://www.gistalliance.com) misleadingly promotes an intended use for the drug for which safety and effectiveness have not been established, thereby causing the approved PI to lack adequate directions for the use recommended in the materials. Specifically, the healthcare professional-directed portion of the website contains numerous claims that promote the neoadjuvant use of Gleevec **before** surgical resection of GIST tumors, a use for which the drug is not indicated. These claims include:

- "Surgical resection is the primary intervention of treatment for GISTs when the tumor is resectable with minimal surgical morbidity. However, when the size and/or location of the tumor makes it inoperable, increases likely morbidity, or renders the tumor only partially resectable, NCCN treatment guidelines call for neoadjuvant treatment with a TKI prior to surgery."<sup>5</sup>
- "Pretreatment with a KIT TKI has been shown to downstage GISTs and/or their metastases and render them resectable in many cases."<sup>6,7,8</sup>
- "The duration of TKI treatment prior to surgical resection is generally based on the radiographic

response to treatment.”

- “Patients who are responding to treatment should be treated until maximal tumor reduction is achieved, which may take 3 to 6 months.”<sup>5</sup>
- “Early surgical intervention is recommended, whenever possible, in patients who have stable disease, as progressive disease is associated with a worse outcome<sup>[8,9]</sup> and tumors may rapidly become unresectable.”<sup>5,8</sup>

These claims are accompanied by a series of PET images showing reduction in tumor mass in a GIST patient at baseline and after 3, 6, and 12 months of neoadjuvant TKI therapy.<sup>6</sup>

We note that these statements do not explicitly include the trade name “Gleevec.” However, the footnoted references clearly indicate the established name of the drug (i.e., imatinib) used in the clinical studies and the text refers readers to the NCCN Treatment Guidelines for GIST tumors, which exclusively recommend the use of imatinib for neoadjuvant GIST therapy. The totality of this presentation misleadingly suggests that Gleevec is safe and effective for the neoadjuvant therapy of GIST tumors.

Similarly, the consumer-directed portion of the website contains the following statements:

- “The term ‘neoadjuvant treatment’ refers to therapy that is given with a goal of reducing the size of a tumor before surgery.”
- “If your GIST is too large to be surgically removed, or if the location of the tumor makes surgery too risky, your doctor may prescribe drug treatment with a TKI.”

Gleevec is not approved for neoadjuvant use in GIST patients (nor is any other drug), and the approved PI for Gleevec does not include any information on the safety and efficacy of this drug when used **before** surgical resection of GIST tumors. Therefore, the webpages suggest a use for Gleevec for which safety and effectiveness has not been established, thereby creating a new intended use for the drug for which the approved PI lacks adequate directions.

### Omission and Minimization of Risk

Promotional materials are misleading if they omit material facts about the consequences that may result from the use of the drug as recommended or suggested by the materials. The websites make prominent claims of effectiveness for Gleevec in GIST and CML, but omit material facts about the considerable risks associated with this drug. For example, the GIST Alliance website makes the following claims about the use of Gleevec in the treatment of GIST tumors:

- “Several investigators, including DeMatteo et al, reported data that showed increased progression-free survival in patients who had received adjuvant TKI treatment after resection of GIST.<sup>[9, 10, 11]</sup> These findings led to a multicenter, placebo-controlled trial to evaluate adjunctive therapy in GIST.”
- “In this trial, patients were randomized to receive daily TKI treatment or placebo for 1 year following complete surgical resection of GIST. Accrual to the study was halted per the recommendation of an independent data monitoring committee based on a planned interim analysis. After a median follow-up of 19.7 months in recurrence-free patients:<sup>[4]</sup>
  - o One-year recurrence-free survival was 98% in the TKI treatment arm vs. 83% with placebo (hazard ratio, 0.35 [95% CI, 0.22 to 0.53]; (P=.0001)
  - o No difference in overall survival was detected, as follow-up time was short and participants in the placebo group were allowed to cross over to active treatment upon recurrence of GIST.”

This presentation, which is based on the clinical study of Gleevec submitted to the FDA for the adjuvant GIST approval, provides data on the efficacy benefits associated with Gleevec, but fails to adequately describe the risks associated with Gleevec. The patient-directed portion of the website also presents information about treatment benefit derived from a Gleevec study, such as:

- "A study of adjuvant treatment in GIST showed that when patients took daily TKI treatment after surgery, very few had a return of GIST—only one patient out of 23 (4%). Among patients who had surgery but did not receive TKI treatment, 32 out of 48 (67%) had a return of GIST—most within 2 years."
- "If you have had a GIST surgically removed, ask your doctor if adjuvant TKI treatment is right for you."

Similarly, the healthcare professional-directed portion of the CML Alliance website makes claims about the use of Gleevec in the treatment of CML, including:

- "Early molecular response may also predict lack of disease progression. Long-term follow-up data in a large TKI clinical trial have shown that 100% of patients who achieved both CCyR and MMR at 12 months remained free from progression to accelerated phase (AP) or blast crisis (BC) at 5 years."<sup>12</sup>

The consumer-directed portion of the website also discusses the benefits of treatment with presentations such as the following:

- "TKI treatment<sup>1</sup> is designed to block the action of BCR-ABL. Without this growth signal, the abnormal cells stop growing and begin to die. Within a few months, healthy cells begin replacing the abnormal cells, and blood returns to its normal mixture of cell types. Treatment for CML is based on class of drugs called tyrosine kinase inhibitors (TKIs)."
- "Click here for prescription treatment information for CML" - this link takes viewers to another Novartis-sponsored webpage that contains information about treatment with Gleevec<sup>2</sup>

Apart from a brief list of examples of supportive care strategies that can be used to address some of the common and mild side effects, there is **no** mention of the serious risks of Gleevec therapy presented on these websites. The websites therefore misleadingly suggest that Gleevec is safer than has been demonstrated by substantial evidence or substantial clinical experience.

### **Unsubstantiated Dosing Claims/Omission of Risk Information**

Both the CML Alliance and GIST Alliance websites make numerous dosing-related claims that are wholly unsubstantiated, and may even put patients at increased risk for serious adverse events. As noted in the Background section, the likelihood of developing an adverse reaction to Gleevec increases with higher doses. However, these sites urge physicians to measure the plasma concentration of tyrosine kinase inhibitor in their patients' blood, and then use that information to individualize the drug's dosage or schedule, while failing to reveal any of the serious or potentially dose-related side effects associated with Gleevec.

For example, the *GIST Alliance – Gastrointestinal Stromal Tumors (GISTs) Blood Level Testing* webpage includes the following statements:

- "Blood level testing, an important component of therapeutic drug monitoring (TDM), involves measuring a drug's concentration in a patient's blood and then using that information to individualize care for your patients."<sup>13</sup>
- "Therapeutic drug monitoring is critical for oral oncology drugs, because oral agents are inherently more susceptible than IV agents to intra- and interpatient variability in absorption, bioavailability,

and adherence.<sup>[14, 15]</sup> Sub therapeutic drug concentrations have been identified as the most important concern relating to the oral administration of anticancer agents."<sup>16</sup>

- "Although TKI treatment has been shown to be an effective treatment for GIST, individual patient results may vary. Blood level testing may help to illuminate causes of inadequate or unexpectedly slow responses to treatment."<sup>17, 18</sup>
- "Studies of TKI Treatment in GIST have shown a correlation between low drug plasma levels and inadequate response to treatment."<sup>17, 18</sup>
- "Suboptimal plasma levels may be due to patient non-adherence, or to other factors, including<sup>[19]</sup>
  - Host differences in drug absorption/metabolism
  - Comorbidities
  - Drug-drug interactions"
- "Establishing a baseline blood level 30 to 90 days after the initiation of therapy can provide a reference point for future measurements and may help the clinician optimize treatment when evaluating response."

*The CML Alliance – Blood Level Testing in the Management of CML* webpage includes the above claims or slightly modified versions of the above claims, in addition to the following:

- "Therapeutic drug monitoring is used to help:
  - Maximize a drug's therapeutic effect<sup>[13]</sup>
  - Minimize toxicity<sup>[13]</sup>
  - Assess patient adherence"<sup>14</sup>

The totality of these presentations suggests that a lack of response in patients may be due to low plasma levels of Gleevec, and that the dose of Gleevec should be modified (i.e., increased) in the event that plasma concentrations of the drug are found to be "suboptimal." FDA is not aware of substantial evidence or substantial clinical experience to support a correlation between patient outcome and plasma levels of imatinib. The PI for Gleevec provides very specific dosage recommendations for Gleevec in CML and GIST, with guidelines for monitoring adverse events and specific instructions for **dose reduction or discontinuation** in the event of serious adverse events (see Background). The PI does not contain a provision for plasma level monitoring of Gleevec in patients, nor does it discuss increasing the dose of Gleevec based on this information. The referenced publications cited on the GIST Alliance webpage do not provide substantial evidence or substantial clinical experience to support these claims. Specifically, only one of the publications referenced<sup>18</sup> to support such an implication is relevant to GIST patients. The Demetri reference is a brief clinical monograph from a supplemental edition of *Clinical Advances in Hematology & Oncology*. The two page monograph references an abstract from the 2008 American Society of Clinical Oncology annual meeting that describes unpublished results of a retrospective subgroup analysis that makes claims about overall survival (OS), as well as correlations between OS and plasma imatinib levels. Such a reference does not constitute substantial evidence or substantial clinical experience in support of such claims. The second referenced article describes an exploratory, uncontrolled, retrospective subgroup analysis of plasma imatinib levels sampled at a single time point in patients with CML and the corresponding clinical responses. These data do not constitute substantial evidence or substantial clinical experience to support the referenced claims.

Furthermore, the suggestion that the dose of Gleevec should be modified in the event that plasma concentrations of the drug are found to be "suboptimal" may put patients at considerable risk of adverse events, many of which are dose-related. The fact that these misleading dosing claims are presented without any discussion of serious or potentially dose-related side effects, such as neutropenia or thrombocytopenia, is grossly misleading and greatly minimizes the potential risk to patients of increasin

the dose. We further note that these websites heavily promote the "CML & GIST Alliance™ Blood Level Testing Program," which encourages physicians to test their patients for "suboptimal" plasma levels of imatinib. Novartis explicitly recommends a laboratory (Avantix Laboratories) to provide the corresponding testing services and provides hyperlinks that physicians can use to access these recommended services. The associated website dedicated to this specific imatinib blood level testing program, [www.bloodleveltesting.com](http://www.bloodleveltesting.com), makes numerous unsubstantiated claims about the use of blood tests to optimize outcomes specifically in patients with GIST or CML who are taking imatinib mesylate. For example, the website includes many claims that are identical to those included on the GIST Alliance and CML Alliance websites (excerpted above). Additional claims correlate patient response with imatinib pharmacokinetics and specific plasma drug levels.,<sup>20</sup>

Although clicking on the prominently displayed links on the CML Alliance and GIST Alliance websites leading to [www.bloodleveltesting.com](http://www.bloodleveltesting.com) produces a pop-up window disclaimer stating that you are "moving to an external website independently operated and not managed by the Novartis Pharmaceuticals Corporation," we note several indicators that Novartis is, in fact, responsible for the content of the website. For example, the website is registered to Novartis AG<sup>21</sup>, contains the CML Alliance and GIST Alliance logos, and makes repeated reference to Novartis. For example, the site includes the statement:

- "Novartis, a global leader in oncology, continues to work with healthcare professionals and patients worldwide to advance the treatment of Ph+ chronic myeloid leukemia (CML) and gastrointestinal stromal tumors (GISTs). CML Alliance™ and GIST Alliance™ are unique support programs created by Novartis to help healthcare professionals optimize outcomes in patients with these conditions."

In addition, the webpages within [www.bloodleveltesting.com](http://www.bloodleveltesting.com) provide hyperlinks to the CML Alliance and GIST Alliance home pages. The website does not mention any TKIs other than imatinib, nor does it mention pharmaceutical manufacturers other than Novartis.

Furthermore, Novartis provides the Blood Level Testing Program at no cost to healthcare providers. Thus, it appears that Novartis may be at least partly responsible for the content on this website. DDMAC is deeply troubled by the content of the [www.bloodleveltesting.com](http://www.bloodleveltesting.com) website and the potential risk to the public health from the multiple dosing implications for imatinib contained on this website.

<sup>20</sup> von Mehren M, Wang Y, Joensuu H, et al. Imatinib pharmacokinetics (PK) and its correlation with clinical response in patients with unresectable/metastatic gastrointestinal stromal tumor (GIST). *J Clin Oncol.* 2008;26(15S):4523.

<sup>21</sup> [www.whois.net](http://www.whois.net) domain-based research services. Accessed January 21 2010; re-"[www.bloodleveltesting.com](http://www.bloodleveltesting.com)."

## **Failure to Submit**

FDA regulations require companies to submit specimens of any labeling or advertising devised for promotion of a drug product approved under Subpart H regulations at least 30 days prior to the intended time of initial dissemination per 21 CFR 314.550. Moreover, FDA regulations require companies to submit specimens of any labeling or advertising devised for promotion of the drug product at the time of initial dissemination of the labeling and at the time of initial publication of the advertisement for a prescription drug product. Each submission is required to be accompanied by a completed transmittal Form FDA-2253 (Transmittal of Advertisements and Promotional Labeling for Drugs and Biologics for Human Use) and is required to include a copy of the product's current professional labeling. These materials were not submitted to FDA 30 days prior to the intended time of initial dissemination or initial publication as required by 21 CFR 314.550, and were not submitted to FDA under cover of Form FDA-2253 at the time of their initial publication, as required by 21 CFR 314.81(b)(3)(i).

## **Conclusion and Requested Action**

For the reasons discussed above, your promotional pieces misbrand Gleevec in violation of the Federal Food, Drug and Cosmetic Act (the Act), 21 U.S.C. 352(a), (f)(1) & (n); 321(n), and FDA implementing regulations. See 21 CFR 201.100(c), 201.115 & 201.128, 21 CFR 202.1(e)(5), (e)(6)(i), (iv) & (xi). In addition, it appears that the websites were neither submitted as required by 21 CFR 314.550, nor submitted to FDA under cover of Form FDA-2253 at the time of their initial publication, as required by 21 CFR 314.81(b)(3)(i).

DDMAC requests that Novartis immediately cease the dissemination of violative promotional materials for Gleevec such as those described above. Please submit a written response to this letter on or before May 5, 2010, stating whether you intend to comply with this request, listing all promotional materials (with the 2253 submission date) for Gleevec that contain violations such as those described above, and explaining your plan for discontinuing use of such violative materials. Because the violations described above are serious we request that your submission include a comprehensive plan of action to disseminate truthful, nonmisleading, and complete corrective messages about the issues discussed in this letter to the audience(s) that received the violative promotional materials.

In addition, we request that you respond with the full details of your involvement with and control over the [www.bloodleveltesting.com](http://www.bloodleveltesting.com) website, which may also be in violation of the Federal Food, Drug, and Cosmetic Act.

Please direct your response to me at the 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, or facsimile at 301-847-8444. In all future correspondence regarding this matter, please refer to MACMIS 18492 in addition to the NDA number. We remind you that only written communications are considered official.

The violations discussed in this letter do not necessarily constitute an exhaustive list. It is your responsibility to ensure that your promotional materials for Gleevec comply with each applicable requirement of the Act and FDA implementing regulations.

Failure to correct the violations discussed above may result in FDA regulatory action, including seizure or injunction, without further notice.

Sincerely,  
{See appended electronic signature page}  
Thomas W. Abrams, RPh, MBA  
Director  
Division of Drug Marketing,  
Advertising, and Communications

<sup>1</sup> As described in more detail below, DDMAC is also concerned with a third website, [www.bloodleveltesting.com](http://www.bloodleveltesting.com), which is linked to the above-mentioned Novartis websites and contains similar dosing claims to these websites.

<sup>2</sup> Although beyond the scope of the issues discussed in this letter, we also note that the healthcare-professional portion of the CML Alliance website provides a direct link to the Tasigna product website in reference to second-line therapy for CML, and that the "My CML Circle Program" page (at [www.mycmlcircle.com](http://www.mycmlcircle.com)) also discusses Tasigna (another Novartis product) as a second-line therapy for CML.

<sup>3</sup> [www.whois.net](http://www.whois.net) domain-based research services. Accessed January 21, 2010; re-"[www.cmlalliance.com](http://www.cmlalliance.com)" and "[www.gistalliance.com](http://www.gistalliance.com)"

<sup>4</sup> DeMatteo RP, Ballman KV, Antonescu CR et al, on behalf of the American College of Surgeons Oncology Group (ACOSOG) Intergroup Adjuvant GIST Study Team. Adjuvant imatinib mesylate after resection of localized, primary gastrointestinal stromal tumor: a randomized, double-blind, placebo-controlled trial. *Lancet*.2009;373:1097-1104.

<sup>5</sup> National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology: soft tissue sarcoma. V.2.2007.

<sup>6</sup> Bummig P, Andersson J, Meis-Kindblom JM, et al. Neoadjuvant, adjuvant and palliative treatment of gastrointestinal stromal tumours (GIST) with imatinib: a centre-based study of 17 patients. *Br J Cancer*. 2003;89(3):460-464.

<sup>7</sup> Radkani P, Gheris MM, Paramo JC, Mesko TW. A multidisciplinary approach for the treatment of GIST liver metastasis. *World J Surg Oncol*. 2008;6:46.

<sup>8</sup> Andtbacka RHI, Ng CS, Scaife CL, et al. Surgical resection of gastrointestinal stromal tumors after treatment with imatinib. *Ann Surg Oncol*. 2007;14(1):14-24.

<sup>9</sup> Gronchi A, Fiore M, Miselli F, et al. Surgery of residual disease following molecular-targeted therapy with imatinib mesylate in advanced/metastatic GIST. *Ann Surg*. 2007;245(3):341-346.

<sup>10</sup> Sym SJ, Ryu MH, Lee JL, et al. Surgical intervention following imatinib treatment in patients with advanced gastrointestinal stromal tumors (GISTs). *J Surg Oncol*. 2008;98(1):27-33.

<sup>11</sup> DeMatteo RP, Maki RG, Singer S, Gonen M, Brennan MF, Antonescu CR. Results of tyrosine kinase inhibitor therapy followed by surgical resection for metastatic gastrointestinal stromal tumor. *Ann Surg*. 2007;245(3):347-352.

<sup>12</sup> Druker BJ, Guilhot F, O'Brien SG, et al. Five-year follow-up of patients receiving imatinib for chronic myeloid leukemia. *N Engl J Med*. 2006;355(23):2408-2417.

<sup>13</sup> Alnaim L. Therapeutic drug monitoring of cancer chemotherapy. *J Oncol Pharm Practice*. 2007;13(4):207-221.

<sup>14</sup> Huguenot PWH, Burger DM, Aarnoutse RE, et al. Therapeutic drug monitoring of HIV-protease inhibitors to assess noncompliance. *Ther Drug Monitor*. 2002;24(5):579-587.

<sup>15</sup> McLeod HL, Evans W. Oral cancer chemotherapy: the promise and the pitfalls. *Clin Cancer Res*. 1999;5(10):2669-2671

<sup>16</sup> Kuppens IEL, Breedveld P, Beijnen JH, Schellens JHM. Modulation of oral drug bioavailability: from preclinical mechanism to therapeutic application. *Cancer Investig*. 2005;23(5):443-464.

<sup>17</sup> Larson RA, Druker BJ, Guilhot F, et al; for IRIS (International Randomized Interferon vs STI571) Study Group. Imatinib pharmacokinetics and its correlation with response and safety in chronic-phase chronic myeloid leukemia: a subanalysis of the IRIS study. *Blood*. 2008;111(8):4022-4028.

<sup>18</sup> Demetri GD. Therapeutic monitoring of drug plasma concentrations and improved outcomes in GIST. *Clin Adv Hem Oncol*. 2009;7(2)(suppl 4):6-7.

<sup>19</sup> Egorin MJ. Promises and pitfalls of oral cancer chemotherapy. *Clin Adv Hem Oncol*. 2009;7(2)(suppl 4):8-10.

<b>Application Type/Number</b>	<b>Submission Type/Number</b>	<b>Submitter Name</b>	<b>Product Name</b>
NDA-21588	ORIG-1	NOVARTIS PHARMACEUTICA LS CORP	GLEEVEC (IMATINIB MESYLATE) 100/400MG

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