

**IMPORTANT
CORRECTION
OF DRUG
INFORMATION
about
Gleevec®
(imatinib mesylate)
Tablets for Oral Use**

September 2010

Dear Health Care Provider:

In a recent Warning Letter to Novartis Pharmaceuticals Corporation, the Division of Drug Marketing, Advertising and Communication (DDMAC) of the Food and Drug Administration (FDA) stated that two of our websites, www.cmlalliance.com and www.gistalliance.com, were misleading because they promoted Gleevec for an unapproved use (neoadjuvant use of Gleevec before surgical resection of GIST tumors), made unsubstantiated dosing claims for Gleevec that may put patients at higher risk of experiencing serious adverse events, and omitted all of the serious risks associated with the use of Gleevec. Novartis takes the FDA Warning Letter very seriously and as a result has suspended these websites and all related materials. Novartis values the safety of patients and believes that providing health care providers and patients access to accurate, timely and relevant disease information on rare diseases is important.

This letter responds to FDA's request to contact you to provide important information to correct the information on the websites that the FDA considered to be misleading promotional messages and presentations about Gleevec as described in the Warning Letter. This letter provides information about the approved uses for Gleevec in patients with Ph+ CML and Kit+ GIST, as well as Important Safety Information for Gleevec.

The FDA stated the www.gistalliance.com website contained claims that promoted the neoadjuvant use of Gleevec before surgical resection of GIST tumors, a use for which the drug is not approved. 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, accelerated 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

Additionally, the FDA stated the www.gistalliance.com and www.cmlalliance.com websites made unsubstantiated claims that suggested that the plasma levels of Gleevec could be directly correlated to patient response. The websites also urged physicians to measure the plasma concentrations of Gleevec and use that information to individualize the drug's dosage or schedule. Appropriate clinical evidence is not available to support a correlation between imatinib plasma levels and patient response. Increasing the dose of Gleevec based on imatinib blood levels may put patients at increased risk for serious adverse events. The PI for Gleevec does not contain a provision for measuring Gleevec plasma concentrations, nor does it discuss titrating the dose of Gleevec based on this plasma level.

Finally, FDA stated the websites omitted all of the serious risks associated with the use of Gleevec in GIST and CML patients. Gleevec is associated with serious risks and these risks increase with higher doses of Gleevec. The Important Safety Information is provided in this letter; however, please be assured that the Gleevec safety information has not changed.

The following information is meant to fully clarify the information described above and not to announce new safety information for Gleevec. There is no change in the risk information regarding the use of Gleevec in CML and GIST.

IMPORTANT DOSAGE AND ADMINISTRATION INFORMATION REGARDING USE OF GLEEVEC IN CML & GIST

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.

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

The likelihood of developing an adverse reaction to Gleevec PI 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 contains 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). In children, daily doses can be reduced under the same circumstances from 340 mg/m²/day to 260 mg/m²/day or from 260 mg/m²/day to 200 mg/m²/day, respectively. 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:

<p>Chronic Phase CML (starting dose 400 mg)</p>	<p>ANC <1.0 X 10⁹ /L and/or</p>	<p>1. Stop Gleevec until ANC ≥1.5 10⁹/L 2. Resume treatment with Gleevec at the original starting dose of 400 mg 3. 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.</p>
<p>GIST (starting dose 400 mg)</p>	<p>platelets <50 X 10⁹/L</p>	

Important Safety Information for Use of Gleevec in CML & GIST Indications

- Gleevec is often associated with edema and occasionally serious fluid retention. Patients should be weighed and monitored regularly for signs and symptoms of fluid retention, which can be serious or life-threatening, and be advised to report any rapid, unexpected weight gain. The probability of edema tended to be increased among older patients (>65 years) or those taking higher doses of Gleevec. If severe fluid retention occurs, Gleevec should be withheld until the event has resolved and then resumed depending on the initial severity of the event.
- Cytopenias have been reported. Complete blood counts should be performed weekly for the first month, biweekly for the second month, and periodically thereafter as clinically indicated (for example, every 2-3 months). Dose reduction or treatment interruption may be required for severe neutropenia or thrombocytopenia (see full Prescribing Information for dose adjustment recommendations).
- Severe congestive heart failure and left ventricular dysfunction have occasionally been reported. Most of the patients with reported cardiac events have had other comorbidities and risk factors, including advanced age and previous medical history of cardiac disease. Patients with cardiac disease or risk factors for cardiac failure should be monitored carefully, and any patient with signs or symptoms consistent with cardiac failure should be evaluated and treated.
- Hepatotoxicity, occasionally severe, 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. A 25% decrease in the recommended dose should be used for patients with severe hepatic impairment. If severe hepatotoxicity occurs, Gleevec should be withheld until the event has resolved and then resumed depending on the initial severity of the event.
- In the newly diagnosed CML trial, 1.8% of patients had (NCI Grades 3/4) hemorrhage. In the Phase 3 unresectable or metastatic GIST studies, 12.9% of patients reported (NCI Grades 3/4) hemorrhage at any site. In the Phase 2 unresectable or metastatic GIST study, 5% of patients were reported to have severe gastrointestinal (GI) bleeds and/or intratumoral bleeds. GI tumor sites may have been the source of GI bleeds.
- In patients with hypereosinophilic syndrome and cardiac involvement, cardiogenic shock and left ventricular dysfunction have been associated with initiation of Gleevec. The condition was reported to be reversible with the administration of systemic steroids, circulatory support measures and temporarily withholding Gleevec. MDS/MPD disease and systemic mastocytosis may be associated with high eosinophil levels. Performance of an echocardiogram and determination of serum troponin should therefore be considered in patients with HES/CEL, and in patients with MDS/MPD or ASM associated with high eosinophil levels. If either is abnormal, the prophylactic use of systemic steroids (1-2 mg/kg) for 1-2 weeks concomitantly with imatinib should be considered at the initiation of therapy.

- Bullous dermatologic reactions (eg, erythema multiforme and Stevens-Johnson syndrome) have also been reported. In some cases, the reaction recurred upon rechallenge. Several postmarketing reports describe patients able to tolerate the reintroduction of Gleevec at a lower dose with or without concomitant corticosteroids or antihistamines following resolution or improvement of the bullous reaction.
- Clinical cases of hypothyroidism have been reported in thyroidectomy patients undergoing levothyroxine replacement during treatment with Gleevec. TSH levels should be closely monitored 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; therefore, women of childbearing potential should be advised to not become pregnant while taking Gleevec tablets and to avoid breast-feeding while taking Gleevec tablets because of the potential for serious adverse reactions in nursing infants. Sexually active female patients taking Gleevec should use adequate contraception. If the patient does become pregnant while taking Gleevec, the patient should be advised of the potential hazard to the fetus.
- In Ph+ CML trials, severe (NCI Grades 3/4) lab abnormalities—including neutropenia (3.6%-48%), anemia (1%-42%), thrombocytopenia (<1%-33%), and hepatotoxicity (approx 5%)—and severe adverse reactions (NCI Grades 3/4), including hemorrhage (1.8%-19%), fluid retention (eg, pleural effusion, pulmonary edema, and ascites) (2.5%-11%) and superficial edema (1.5%-6%), and musculoskeletal pain (2%-9%) were reported among patients receiving Gleevec. Severe fluid retention appears to be dose-related, was more common in the advanced phase studies (where the dosage was 600 mg/day), and is more common in the elderly.
- In the Phase 2 unresectable or metastatic GIST trial (400 mg; 600 mg/day) severe (NCI Grades 3/4) lab abnormalities—including anemia (3%; 9%) and neutropenia (10%; 11%)—were reported among patients receiving Gleevec. In Phase 3 unresectable or metastatic GIST trials (400 mg/day; 800 mg/day) severe adverse reactions (NCI Grades 3/4/5), including abdominal pain (14%; 12%), edema (9%; 13%), fatigue (12%; 12%), nausea (9%; 8%), vomiting (9%; 8%), diarrhea (8%; 9%), rash (8%; 9%), and myalgia (6%; 4%) were reported among patients receiving Gleevec.
- In the adjuvant treatment of GIST trials (Gleevec; placebo) severe (NCI Grades 3 and above) lab abnormalities—increased liver enzymes (ALT) (3%; 0%), (AST) (2%; 0%), decreased neutrophil count (3%; 1%), and decrease in hemoglobin (1%; 0%)—and severe adverse reactions (NCI Grades 3 and above), including abdominal pain (3%; 1%), diarrhea (3%; 1%), rash (3%; 0%), fatigue (2%; 1%), nausea (2%; 1%), vomiting (2%; 1%), white blood cell count decreased (1%; 0%), and periorbital edema (1%; 0%) were reported among patients receiving adjuvant treatment with Gleevec.

- There have also been reports, including fatalities, of cardiac tamponade, cerebral edema, acute respiratory failure, and gastrointestinal perforation.
- Gleevec is metabolized by the CYP3A4 isoenzyme and is an inhibitor of CYP3A4, CYP2D6, and CYP2C9. Significant reductions in imatinib concentrations may occur when Gleevec is administered concomitantly with agents that are strong CYP3A4 inducers such as rifampin, St John's wort, and enzyme-inducing anti-epileptic drugs e.g., phenytoin. The use of concomitant strong CYP3A4 inducers should be avoided. If patients must be administered a strong CYP3A4 inducer, the dosage of Gleevec should be increased by at least 50% and clinical response should be carefully monitored. Caution is recommended when Gleevec is administered with CYP3A4 inhibitors such as ketoconazole, with CYP2D6 substrates that have a narrow therapeutic window, or with CYP3A4 substrates that have a narrow therapeutic window. Other, examples of commonly used drugs that may significantly interact with Gleevec include acetaminophen, warfarin, erythromycin, and metoprolol. Grapefruit juice should also be avoided in patients taking Gleevec. (Please see full Prescribing Information for other potential drug interactions.)
- Patients with moderate renal impairment (CrCL = 20-39 mL/min) should receive a 50% decrease in the recommended starting dose and future doses can be increased as tolerated. Doses greater than 600 mg are not recommended in patients with mild renal impairment (CrCL = 40-59 mL/min). For patients with moderate renal impairment, doses greater than 400 mg are not recommended. Gleevec should be used with caution in patients with severe renal impairment.
- For daily dosing of 800 mg and above, dosing should be accomplished using the 400-mg tablet to reduce exposure to iron.

Please see enclosed full prescribing information for Gleevec (imatinib mesylate) Tablets.

If you have any questions about Gleevec, please contact our Medical information Center at 1-888-NOW-NOVARTIS (1-888-669-6682).

Sincerely,



John Hohneker, MD
Senior Vice President, US Clinical Development & Medical Affairs- Oncology