DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-335/S-006

Novartis Pharmaceuticals Corporation
One Health Plaza, Building 105/2W200
Hanover, New Jersey 07936-1080

Attention: Robert A. Miranda, Director
Drug Regulatory Affairs

Dear Mr. Miranda:

Please refer to your supplemental new drug application dated April 30, 2003, received May 2, 2003, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Gleevec (imatinib mesylate) Capsules, 100 mg.

We acknowledge receipt of your submissions dated May 2 and July 10, 2003 and correspondences dated October 28 and 29, 2003.

This "Changes Being Effected" supplemental new drug application provides for additional information to be included in the Post Marketing Experiences subsection of the ADVERSE REACTIONS section of the package insert.

We completed our review of this supplemental new drug application, as amended. It is approved, effective on the date of this letter, for use as recommended in the final printed labeling (FPL) submitted on April 30, 2003.

However, we remind you of your October 28 and 29, 2003 agreement to make the following changes to the package insert at the next printing or within 6 months, whichever comes first.

1. Under **PRECAUTIONS**, **General** subsection, the following paragraph should be added as the first paragraph and read as follows:

   Dermatologic Toxicities:
   Bullous dermatologic reactions, including erythema multiforme and Stevens Johnson syndrome, have been reported with use of Gleevec. In some cases reported during post-marketing surveillance, a recurrent dermatologic reaction was observed upon rechallenge. Several foreign post-marketing reports have described cases in which patients tolerated the reintroduction of Gleevec therapy after resolution or improvement of the bullous reaction. In these instances, Gleevec was resumed at a dose lower than that at which the reaction occurred and some patients also received concomitant treatment with corticosteroids or antihistamines.

2. Under **ADVERSE REACTIONS,** following the **Gastrointestinal Stromal Tumors** subsection, the following subsection should read as:

Additional Data From Multiple Clinical Trials

The following less common (estimated 1%-10%), infrequent (estimated 0.1%-1%), and rare (estimated less than 0.1%) adverse events have been reported during clinical trials of Gleevec. These events are included based on clinical relevance.

Cardiovascular: *Infrequent*: cardiac failure, tachycardia, hypertension, hypotension, flushing, peripheral coldness

Clinical Laboratory Tests: *Infrequent*: blood CPK increased, blood LDH increased

Dermatologic: *Less common*: dry skin, alopecia *Infrequent*: exfoliative dermatitis, bullous eruption, nail disorder, skin pigmentation changes, photosensitivity reaction, purpura *Rare*: vesicular rash, Stevens-Johnson syndrome, acute generalized exanthematous pustulosis

Digestive: *Less common*: abdominal distension, gastroesophageal reflux, mouth ulceration *Infrequent*: gastric ulcer, gastroenteritis, gastritis *Rare*: colitis

Hematologic: *Infrequent*: pancytopenia *Rare:* aplastic anemia

Hypersensitivity: *Rare*: angioedema

Infections: *Infrequent*: sepsis, herpes simplex, herpes zoster

Metabolic and Nutritional: *Infrequent*: hypophosphatemia, dehydration, gout, appetite disturbances, weight decreased *Rare*: hyperkalemia, hyponatremia

Musculoskeletal: *Less common*: joint swelling *Infrequent*: sciatica, joint and muscle stiffness

Nervous System/Psychiatric: *Less common*: paresthesia *Infrequent*: depression, anxiety, syncope, peripheral neuropathy, somnolence, migraine, memory impairment *Rare*: increased intracranial pressure, cerebral edema (including fatalities)

Renal: *Infrequent*: renal failure, urinary frequency, hematuria

Reproductive: *Infrequent*: breast enlargement, menorrhagia, sexual dysfunction

Respiratory: *Rare*: interstitial pneumonitis, pulmonary fibrosis

Special Senses: *Less common*: conjunctivitis, vision blurred *Infrequent*: conjunctival hemorrhage, dry eye, vertigo, tinnitus *Rare*: macular edema, papilledema, retinal hemorrhage

If you issue a letter communicating important information about this drug product (i.e., a "Dear Health Care Professional" letter), we request that you submit a copy of the letter to this NDA and a copy to the following address:

MEDWATCH, HFD-410
FDA
5600 Fishers Lane
Rockville, MD 20857

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

If you have any questions, call Ann Staten, Regulatory Project Manager, at (301) 594-0490.

Sincerely,

{See appended electronic signature page}

Richard Pazdur, M.D.
Director
Division of Oncology Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

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

/s/

Grant Williams
10/31/03 02:27:42 PM
for Dr. Pazdur