Report from the FDA

Approval Summary: Imatinib Mesylate in the Treatment of Metastatic and/or Unresectable Malignant Gastrointestinal Stromal Tumors[1]

Ramzi Dagher,[2] Martin Cohen, Gene Williams, Mark Rothmann, Jogarao Gobburu, Gabriel Robbie, Atiqur Rahman, Gang Chen, Ann Staten, Donna Griebel, and Richard Pazdur

Division of Oncology Drug Products [R. D., M. C., A. S., D. G., R. P.], Division of Pharmaceutical, Evaluation 1 [G. W., J. G., G. R., A. R.], Division of Biometrics 1, Center for Drug Evaluation and Research [M. R., G. C.], United States Food and Drug Administration, Rockville, Maryland 20857

Abstract

Purpose: **Imatinib mesylate (Gleevec; Novartis, East Hanover, NJ) is a receptor tyrosine kinase inhibitor approved previously in 2001 by the United States Food and Drug Administration for the treatment of chronic myelogenous leukemia in blast crisis, accelerated phase, or in chronic phase after failure of IFN-α therapy. We review herein the clinical profile of this drug and the regulatory review leading to the approval of a supplemental New Drug Application for the treatment of metastatic and/or unresectable malignant gastrointestinal stromal tumors (GISTs).**

Experimental Design: **We discuss the efficacy and side effects of imatinib mesylate in a Phase II trial of 147 patients with metastatic and/or unresectable malignant GISTs, the basis for marketing approval, and postmarketing commitments by the drug's manufacturer.**

Results: **Imatinib was assessed in a single, open-label trial involving one European center and three centers in the United States. Seventy-three patients were randomly allocated to receive 400 mg of imatinib daily, and 74 patients received 600 mg daily. At the study report cutoff date, an objective response was confirmed in 56 patients; the overall response rate for the combined study arms was 38% (95% confidence interval, 30–46%). These responses were all partial responses. There was no statistically significant difference in response rates between the two dose groups. Adverse events included edema, fluid retention, nausea, vomiting, diarrhea, myalgias, skin rash, bone marrow suppression, bleeding, and elevations in aspartate aminotransferase, alanine aminotransferase, or bilirubin. Bleeding into the gastrointestinal tract or intratumoral sites occurred in 7 patients (5%) and was not correlated with thrombocytopenia or tumor bulk. The pharmacokinetics of imatinib in GIST patients were similar to those of chronic myelogenous leukemia patients.**

Conclusions: **On February 1, 2001, imatinib mesylate was approved by the United States Food and Drug Administration for the treatment of malignant metastatic and/or unresectable GISTs. The recommended dose is 400 or 600 mg daily.**

Introduction

GISTs[3] are soft tissue sarcomas thought to arise from mesenchymal stem cells within the GI tract. Although their capacity for metastatic spread cannot be clearly inferred from histopathological features alone, over one-third of all GISTs are malignant (1). These tumors are usually located in the stomach and small intestine; however, they may occur throughout the GI tract (2). The 5-year survival for malignant GI mesenchymal tumors varies widely and has been reported to be from 28 to 80% (2–5). Median survival of patients in whom complete surgical resection is not possible is 10–23 months (3, 4). The median survival from the time of diagnosis of metastatic or recurrent disease has been reported from 12 to 19 months (3, 4).

Chemotherapy regimens have not proven effective in the treatment of GIST tumors. Although anthracycline-based regimens have resulted in response rates of 10–30% for other soft tissue sarcomas, the response rate of GISTs to these regimens has been reported to be 0–5% (4, 5). Radiation therapy has not been shown to be effective.

In addition to histological considerations, molecular biology and immunohistochemistry advances currently provide more specific criteria for the diagnosis of GISTs based on the expression of the cell surface marker CD117 (6). CD117 is an epitope on the extracellular domain of the transmembrane tyrosine kinase receptor Kit, the product of the proto-oncogene c-kit (7). CD117 can be detected on the cell surface of malignant GIST tumor tissues in 95–100% of cases examined. GIST tumors have been hypothesized to harbor c-*kit* oncogene mutations, and these mutations have been demonstrated in a number of CD117-positive GIST tumors (8–10). These commonly include activating mutations of exon 11 and rarely, exons 9 and 13 (11). The inability to detect a mutation in every GIST tumor

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[1] The views expressed are the result of independent work and do not necessarily represent the views and findings of the United States Food and Drug Administration.

[2] To whom requests for reprints should be addressed, at Food and Drug Administration, HFD-150, 5600 Fishers Lane, Rockville, MD 20857. Phone: (301) 827-1535; Fax: (301) 594-0499; E-mail: dagherr@cder.fda.gov.

[3] The abbreviations used are: GIST, gastrointestinal stromal tumor; GI, gastrointestinal; CML, chronic myelogenous leukemia; EORTC, European Organization for Research and Treatment of Cancer; NCI, National Cancer Institute; PS, performance status; SWOG, Southwest Oncology Group; PR, partial response; FDA, Food and Drug Administration; PK, pharmacokinetics; NDA, New Drug Application; AUC, area under the curve.

may reflect the current inability to characterize all mutations and variability of mutation expression in different samples.

Imatinib mesylate (Gleevec; Novartis, East Hanover, NJ) is a protein-tyrosine kinase inhibitor that inhibits the Bcr-Abl tyrosine kinase, the constitutive abnormal tyrosine kinase created by the Philadelphia chromosome in CML. This drug also inhibits the receptor tyrosine kinases for platelet-derived growth factor and stem cell factor, c-Kit.

Joensuu *et al.* (12) first reported the use of imatinib in a patient with a recurrent, metastatic GIST, a 50-year-old female whose tumor demonstrated staining for CD117. She exhibited a response to 400 mg of imatinib daily that was sustained for 11 months at the time of the case report publication.

The submitted GIST trial was initially designed as a pilot study in which two doses of imatinib were explored in an open label, randomized fashion (400 and 600 mg daily). On the basis of responses observed early in the study, the trial was subsequently expanded to a total population of 147 patients. A preliminary report of this trial was presented at the American Society of Clinical Oncology meeting in April 2001 (13).

Other clinical experience with the use of imatinib in patients with GISTs includes a recently completed Phase I dose escalation study conducted by the EORTC (14, 15). In this study, doses ranging from 300 mg daily up to 500 mg twice a day were studied in 36 patients with GISTs and 4 patients with other soft tissue sarcomas. Dose-limiting toxicities consisting of vomiting, nausea, edema, or dyspnea were encountered in 5 patients treated with 500 mg twice a day. A dose of 400 mg twice a day was well tolerated in this population. The NCI and the EORTC are independently conducting randomized multicenter trials of imatinib mesylate, 400 mg/day *versus* 800 mg/day, in GIST patients. After accrual of >700 patients, the intergroup study sponsored by the NCI ceased enrollment in September 2001.

Trial Design

Patients with histologically confirmed malignant metastatic and/or unresectable GISTs were enrolled. Immunohistochemical documentation of c-kit (CD-117) expression in tumor was required.[4] Eligibility criteria required the presence of at least one site of measurable disease (as defined by SWOG solid tumor response criteria) that had not been previously embolized or irradiated. Eastern Cooperative Oncology Group PS had to be ≤3 (16). Patients were excluded if they had received chemotherapy within 4 weeks of enrollment or had received radiotherapy to ≥25% of the bone marrow. Overall objective tumor response rate was the primary end point.

Patients were randomly allocated to receive imatinib by oral single daily dosing at 400 or 600 mg for an exposure period of not more than 24 months, provided that the patient was benefiting from treatment and in the absence of safety concerns.

Because imatinib is a GI irritant, patients were instructed to ingest the drug in a sitting position with a large glass of water. Prophylactic loperamide was recommended for patients who developed grade 1 or 2 diarrhea. Dose modification guidelines were provided in the protocol, and toxicity was graded using the NCI Common Toxicity Criteria version 2.0.[5]

Patients who had disease progression while receiving 400 mg daily were allowed to increase the dose to 600 mg daily. Patients who progressed on 600 mg daily were to be discontinued from the study.

Tumor evaluation was performed at baseline and was planned at the beginning of months 2, 4, 7, 14, 19, and 25 (end of study). Assessments were performed by either magnetic resonance imaging or computed tomography scans. Tumor response was defined by the SWOG solid tumor response criteria (16). All complete and PRs were to be confirmed by a second assessment a minimum of 4 weeks later.

Table 1 Tumor response by dose

Patients	*n*	Confirmed PR *n* (%)	95% confidence interval
At 400 mg daily	73	24 (33%)	22–45%
At 600 mg daily	74	32 (43%)	32–55%
Total	147	56 (38%)	30–46%

Results

Demographics. A total of 147 patients were enrolled at three United States centers and one center in Finland. Seventy-three patients were randomized to receive an imatinib dose of 400 mg daily and 74 to receive 600 mg daily. There were 83 males and 64 females enrolled. The median age at enrollment was 54 years. Eighty-one % of patients had an Eastern Cooperative Oncology Group PS of 0 or 1, 18% had a PS of 2, and a single patient had a PS of 3.

The small intestine and stomach were the most common primary tumor sites. Ninety-eight % of patients had had prior surgery for GIST. Fifty-one % had received prior chemotherapy, and 15% had received prior radiotherapy. Recurrent disease was noted in 90% at study entry.

Efficacy. The FDA requested submission of baseline and best-response radiographic studies for patients classified as responders. Radiographic studies for 59 patients with confirmed responses and 31 patients with unconfirmed responses were submitted.

Using SWOG criteria as described in the protocol, Division of Oncology Drug Products medical officers reviewed all submitted baseline and best-response radiographs. Radiographs were reviewed with a consultant radiologist. The review confirmed PRs in 56 patients, corresponding to an overall response rate of 38% across the two dose levels with a 95% confidence interval of 30–46%. Table 1 summarizes response rate by dose per FDA analysis.

The tumor response rate for the 400-mg dose group was 33%, with a 95% confidence interval of 22–45%. The response

[4] Immunohistochemistry was routinely performed with Kit antibody (A-4052, rabbit polyclonal antiserum, 1:100; DAKO Corp., Carpinteria, CA) according to analysis by an avidin-biotin peroxidase complex method after antigen retrieval.

[5] Toxicity criteria can be viewed at www.ctep.cancer. gov.

Table 2 Drug exposure

Duration of exposure	Initial dose, 400 mg/day (n = 73)	Initial dose, 600 mg/day (n = 74)	All doses (n = 147)
≤6 months	58 (79%)	54 (73%)	112 (76%)
>6 to ≤12 months	15 (21%)	20 (27%)	35 (24%)
Total	73 (100%)	74 (100%)	147 (100%)

rate for the 600-mg dose group was 43%, with a 95% confidence interval of 32–55%. The 95% confidence interval for the difference in tumor response rates (400−600 mg) was (−26 to 5%).

The response rates in the male and female populations were 35% (29−83) and 42% (27 of 64), respectively. The 56 patients with confirmed PRs ranged in age from 28 to 79 years with a median of 55 years, compared with a median age of 54 years in the total study population of 147 patients.

By FDA analysis, response duration ranged from 7 to 38 weeks, with a median of 13 weeks. At the study report cutoff date, 55 of 56 patients with confirmed PRs had maintained ongoing PRs. One of 56 patients had documented disease progression by the cutoff date. This patient remained on treatment, despite evidence of disease progression, and on subsequent imaging was found to have renewed evidence of a PR. The time from first diagnosis of a response to the last successive confirmation of a response in this patient was 142 days. The majority of patients with a confirmed PR had response onset by day 89 after initiation of imatinib. Further follow-up will be required for more accurate estimations of time to onset of response and response duration.

Safety. Table 2 summarizes imatinib exposure by the FDA's assessment. At the last assessment date, the majority of patients had a duration of exposure of ≤6 months. In addition to the 147 patients with GISTs, the FDA had previously reviewed safety data from 1110 patients treated with imatinib at similar doses and schedules for CML in one Phase I trial and three Phase II trials of imatinib in accelerated phase, chronic phase, and blast crisis CML.

Serious adverse events were reported in 29% of patients in the GIST safety database. Similar to the CML database, grade 3 or 4 fluid retention, edema, diarrhea, vomiting, abdominal pain, and hepatotoxicity were observed in GIST patients. Table 3 summarizes adverse events observed in the trial.

Bleeding was noted in 25 (17%) patients. Of these, 7 had hemorrhages into the GI tract or tumor sites, and a single patient had a cerebral event. Bleeding did not correlate with imatinib dose, platelet count, tumor burden, or treatment duration. Hemorrhages may have reflected tumor rupture into the lumen of the stomach or small intestine. Sixteen of these 25 patients had less severe bleeding episodes (*e.g.*, subconjunctival hemorrhages or guaiac-positive stools).

Extremity and facial edema occurred commonly in patients with GISTs, reported in 36.1 and 59.2% of all patients, respectively. Ascites or pleural effusion was uncommon, reported in 2% of all patients. Grade 3 or 4 edema was uncommon, reported in 5% of all patients in the study. There was no relationship between dose and severity of edema.

Table 3 Adverse experiences reported in the GIST trial[a]

Initial dose (mg/day)	All grades		Grade 3 or 4	
Preferred term	400 mg (n = 73) %	600 mg (n = 74) %	400 mg (n = 73) %	600 mg (n = 74) %
Fluid retention	71	76	6	3
Superficial edema	71	76	4	0
Pleural effusion or ascites	6	4	1	3
Diarrhea	56	60	1	4
Nausea	53	56	3	3
Fatigue	33	38	1	0
Muscle cramps	30	41	0	0
Abdominal pain	37	37	7	3
Skin rash	26	38	3	3
Headache	25	35	0	0
Vomiting	22	23	1	3
Musculoskeletal pain	19	11	3	0
Flatulence	16	23	0	0
Any hemorrhage	18	19	5	8
Tumor hemorrhage	1	4	1	4
Cerebral hemorrhage	1	0	1	0
GI tract hemorrhage	6	4	4	1
Nasopharyngitis	12	14	0	0
Pyrexia	12	5	0	0
Insomnia		11	0	0
Back pain	11	10	1	0
Lacrimation increased	6	11	0	0
Upper respiratory tract infection	6	11	0	0
Taste disturbance	1	14	0	0

[a] All adverse events occurring in ≥10% of patients are listed, regardless of suspected relationship to treatment.

Aspartate aminotransferase or alanine aminotransferase elevations were noted in 49.7 and 34% of all patients, respectively. Grade 3 or 4 elevations in bilirubin occurred in 4 (2.7%) patients. All 4 had hepatic metastases, as did all patients with grade 3 or 4 elevations in aspartate aminotransferase or alanine aminotransferase.

Although anemia, neutropenia, and thrombocytopenia occurred commonly in GIST patients treated with imatinib (94.6, 42.9, and 23.1%, respectively), grade 3 or 4 hematological abnormalities were observed infrequently (anemia, 4.8%; neutropenia, 7.5%; thrombocytopenia, 1%). The relatively decreased severity of hematological toxicity in GIST patients compared with those with CML may be attributed to the lack of underlying bone marrow pathology in GIST patients.

The most common nonhematological events were GI toxicities, including nausea and diarrhea in 55 and 58% of patients, respectively. After fluid retention, diarrhea was the most common adverse event observed.

At the study report cutoff date, 10 patients had died, 7 (9.6%) on the 400-mg arm and 3 (4.1%) on the 600-mg arm. Six deaths were attributed to progressive disease, 3 in each dose group. Four additional patients, all in the 400-mg cohort, suffered fatal adverse events: pulmonary embolism (1), respiratory failure (1), cerebrovascular accident (1), and cardiac arrest (1).

Clinical Pharmacology

The PK characteristics have been described in the CML NDA approved on May 10, 2001 (17). The human PK and

bioavailability data submitted with the GIST supplemental application consisted of one clinical study with PK assessment in GIST patients and one drug-drug interaction study in CML patients completed after the original NDA submission.

Basic PK Properties. In healthy subjects and in population PK studies in >500 patients with CML, imatinib C_{max} was achieved within 2–4 h after the dose. After oral administration in healthy volunteers, the imatinib elimination half-life was ~18 h. The mean AUC increased proportionally with increasing dose over the range of 25–1000 mg. There was no significant change in PK on repeat dosing. The PK of imatinib in GIST patients receiving once-daily dosing (10 at 400 mg and 9 at 600 mg) were similar to those of CML patients.

Drug-Drug Interactions. In a drug interaction study with simvastatin in CML patients, imatinib increased the mean C_{max} and AUC of simvastatin by 2–3-fold, indicating an inhibition of CYP3A4 by imatinib. Therefore, imatinib can increase exposure to comedications that are substrates of CYP3A4.

The CML application identified a significant increase in imatinib exposure in healthy subjects when the drug was coadministered with a single dose of ketoconazole (mean C_{max} increased by 26%, and the AUC increased by 40%), a powerful inhibitor of CYP3A4. This result suggests that coadministration of imatinib with inhibitors of CYP3A4 may increase imatinib exposure.

Hepatic and Renal Impairment. Imatinib and its metabolites are not excreted by the kidneys to any significant extent. Specific studies have not been performed in patients with impaired renal function. Imatinib exposure may increase if liver function is impaired. A PK study in CML patients with liver impairment is currently under way.

Special Populations. There is no effect of gender on imatinib PK in patients with CML or GIST. In CML patients, imatinib clearance appears to increase with increasing body weight. Changes were not considered sufficient to warrant dose adjustment based on body weight. In patients with GISTs, no significant effect of body weight on clearance was evident.

Population PK. Population PK modeling attempted to attribute interpatient PK variability to patient characteristics. Modeling of the GIST dataset by either the sponsor or FDA indicated that patient attributes could not reasonably explain interpatient variability in PK parameters.

Dosing

In CML patients, the recommended dosage is 400 mg/day for patients in chronic phase and 600 mg/day for patients in accelerated phase or blast crisis. A dose of 400 mg daily or 600 mg daily was approved in GIST patients. In the GIST clinical trial, patients were randomized to a dose of 400 or 600 mg/day. The trial was not powered to detect a statistically significant difference in response rates between the two dose levels, and no statistically significant difference was observed. Small differences in the safety profile between the two dose levels studied did not permit a conclusion that the risk:benefit ratio of one dose level was superior.

GIST patients with progressive disease treated with 400 mg daily were allowed to have a dose increase to 600 mg daily. Of 12 patients randomized to 400 mg daily and had dose increases to 600 mg daily for progressive disease, none had subsequent confirmed complete responses or PRs. With the limited follow-up in the study, the relevance of stable disease reported in two patients is unclear.

The EORTC Phase I study of imatinib in patients with GIST and soft tissue sarcomas consisted of dose escalations up to a dose of 500 mg twice daily (1000 mg/day). At this dose level, 3 patients had grade 3 nausea/vomiting, 1 had grade 3 edema, and 1 had grade 3 dyspnea. Dosing at 400 mg twice daily (800 mg/day) was well tolerated, with dose-limiting neutropenia noted in a single patient. Further information regarding efficacy and safety of the 800-mg/day dose in GIST patients will be available from the current NCI- and EORTC-sponsored trials. These trials randomly allocate GIST patients to either 400 or 800 mg/day of imatinib.

Regulatory Basis for Approval

Subpart H (21 CFR 314) allows accelerated approval for serious or life-threatening diseases. For indications where the drug appears to provide benefit over available therapy, accelerated approval may be granted on the basis of a surrogate end point reasonably likely to predict clinical benefit. After approval, the sponsor is required to perform a postmarketing study to demonstrate that treatment is associated with clinical benefit.

For this sNDA, objective response rate was considered a surrogate end point. The pooled response rate of 38% observed in the study (33% for the 400-mg dose group and 43% for the 600-mg dose group) served as the basis for accelerated approval. In the disease setting of malignant, inoperable, and/or metastatic GISTs, where standard chemotherapy is expected to yield a response rate no more than 0–5% and radiation therapy has not been demonstrated to be of benefit, an objective tumor response was considered reasonably likely to predict benefit. The relatively short duration from study initiation to the cutoff date did not allow for an adequate evaluation of response duration, but 55 of 56 confirmed responders had continuing PRs at the time of data cutoff.

Phase IV Postmarketing Commitments

The sponsor has agreed to complete follow-up of the GIST trial described above and submit mature data on response rate, response duration, and survival. A commitment to submit data from the NCI and EORTC multicenter trials is also a mandatory requirement. The sponsor has also agreed to assure the availability of a validated test kit for immunohistochemical detection of CD117 tumor expression.

Other commitments include data submission correlating c-kit expression with response and survival, correlation between serum vascular endothelial growth factor levels and tumor response, and tumor c-kit phosphorylation status before and after exposure to imatinib. Because of the observed GI and tumor hemorrhage observed in this patient population, a Phase IV commitment to investigate the incidence and etiology of GI hemorrhage associated with imatinib therapy has been made.

Conclusions

Imatinib mesylate was approved by the FDA for the treatment of malignant metastatic and/or unresectable GISTs on

February 1, 2002. The approved dose for GIST patients is 400 or 600 mg daily.

Mandatory information requested from the sponsor (Phase IV commitments) includes documentation of response duration and survival, dosing information from current randomized trials, and the prognostic relevance of tumor mutation status.

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