

Report from the FDA**Approval Summary for Imatinib Mesylate Capsules in the Treatment of Chronic Myelogenous Leukemia**

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Abstract

Purpose: Chronic myelogenous leukemia (CML) results from the breakpoint cluster region-Abl fusion gene product, a tyrosine kinase involved in cell division and apoptosis. Imatinib, an orally administered inhibitor of the breakpoint cluster region-Abl tyrosine kinase, is capable of blocking proliferation and inducing apoptosis in CML cell lines. In this report, we describe the preclinical profile of imatinib and the data submitted in the New Drug Application that led to its marketing approval.

Experimental Design: Chemistry manufacturing and controls, animal toxicology, and biopharmaceutical data are described. Results of Phase I and Phase II clinical studies in patients with CML in blast crisis (CML-BC), in accelerated phase (CML-AP), and in chronic phase disease-resistant or intolerant to IFN- α (CML-CP) are summarized. The basis for marketing approval and postmarketing commitments by the pharmaceutical company are discussed.

Results: Toxicology studies in the rat, dog, and monkey show the hematological, renal, and hepatobiliary toxicity of imatinib. Pharmacokinetic studies in patients with CML demonstrate 98% imatinib bioavailability. The elimination half-lives of the parent drug and the major active metabolite, CGP74588, from plasma are approximately 18 and 40 h, respectively. Approximately 81% of the drug is eliminated in 7 days, 68% in the feces and 13% in the urine. Cytochrome P-450 3A4 is the main enzyme responsible for imatinib metabolism. Phase I and II clinical studies were conducted. The Phase I study, in 83 CML patients, evaluated oral imatinib doses from 25 to 1000 mg/day. Dose-limiting toxicity was not observed. The three Phase II studies, in CML-CP, CML-AP, and CML-BC, enrolled 1027 patients. CML-CP patients received 400 mg/day imatinib, whereas CML-AP and CML-BC

patients generally received 600 mg/day imatinib. Primary study endpoints were cytogenetic response rate (CML-CP) and hematological response rate (CML-AP and CML-BC). The cytogenetic response rate for CML-CP patients was 49%. The hematological response rate of CML-AP and CML-BC patients was 63 and 26%, respectively. The most common imatinib adverse events were nausea, vomiting, myalgia, edema, and diarrhea. Elevated liver enzymes and/or bilirubin were reported in 27 patients (2.6%).

Conclusions: On May 10, 2001, imatinib mesylate (Gleevec, formerly known as STI-571 and Glivec), manufactured and distributed by Novartis Pharmaceuticals, East Hanover, NJ, was approved by the United States Food and Drug Administration for the treatment of CML in three clinical settings: CML-BC, CML-AP, and CML-CP. This report summarizes the Food and Drug Administration's review of the New Drug Application.

Introduction

CML² results from the neoplastic transformation of a primitive hematopoietic stem cell. The disease, affecting all hematopoietic cell lineages, is initially characterized by myeloid hyperplasia, basophilia, and splenomegaly (1, 2). The disease progresses through three phases: an initial chronic phase with a median duration of 3–5 years (3), a variably defined accelerated phase lasting 6–18 months (4), and a final blast crisis or acute leukemic phase lasting 3–6 months (4).

CML is characterized by the presence of an abnormally short chromosome 22 (Ph chromosome), resulting from a reciprocal translocation involving the long arms of chromosomes 9 and 22 (5, 6). The Ph chromosome links the Bcr of chromosome 22 with the Abl proto-oncogene of chromosome 9. The normal Abl gene product is a tightly regulated tyrosine kinase involved in cell division and apoptosis. The Bcr-Abl fusion gene product is a constitutively active tyrosine kinase, the presence of which appears sufficient to induce leukemia in both experimental animals and humans (7–9).

Imatinib (Gleevec; Novartis Pharmaceuticals, East Hanover, NJ) is an orally administered protein-tyrosine kinase inhibitor of the Bcr-Abl protein-tyrosine kinase (10–12). The drug blocks proliferation and induces apoptosis of Bcr-Abl-expressing CML and acute lymphocytic leukemia cell lines. Similar

² The abbreviations used are: CML, chronic myelocytic leukemia; CML-AP, CML-accelerated phase; CML-BC, CML-blast crisis; CML-CP, CML-chronic phase after failure of IFN- α therapy; Ph chromosome, Philadelphia chromosome; Ph+, Ph chromosome positive; Bcr, breakpoint cluster region; FDA, Food and Drug Administration; AUC, area under the curve; CYP3A4, cytochrome P-450 3A4; HR, hematological response; CHR, complete HR; NEL, no evidence of leukemia; RTC, return to chronic phase; MCyR, major cytogenetic response; CCyR, complete cytogenetic response; AE, adverse event; NDA, New Drug Application; BM, bone marrow.

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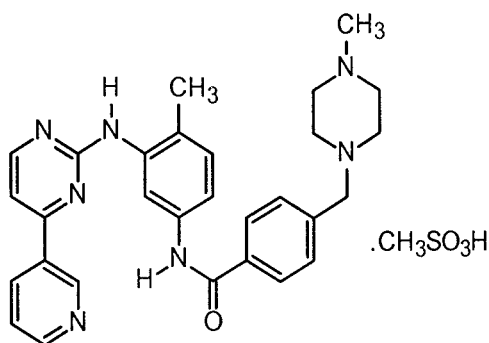


Fig. 1 Structure of imatinib mesylate.

effects were observed using fresh leukemic cells from Ph+ CML and acute lymphocytic leukemia patients. In animal models, the drug displays potent antitumor activity against Bcr-Abl- and v-Abl-expressing cells at tolerated doses. In addition, the drug is a potent inhibitor of the receptor tyrosine kinases for platelet-derived growth factor, stem cell factor, and c-Kit (13). These latter actions provide the rationale for the antitumor activity of the drug in gastrointestinal stromal tumors and possibly other cancers and may explain some of its adverse effects.

Chemistry

Imatinib mesylate is the active component of Gleevec. Imatinib mesylate is designated chemically as 4-[[4-(4-methyl-1-piperazinyl)methyl]-N-[4-methyl-3-[[4-(3-pyridinyl)-2-pyrimidinyl]aminophenyl] benzamide methanesulfonate. Imatinib mesylate is a white to off-white to brownish- or yellowish-tinged crystalline powder. Its molecular formula is $C_{29}H_{31}N_7O \cdot CH_4SO_3$, and its relative molecular mass is 589.7.

The active ingredient is prepared by a multistep synthesis, and its structure is shown in Fig. 1. Imatinib mesylate shows good aqueous solubility at low pH (<5.5) but is poorly soluble or insoluble at neutral and alkaline pH. In nonaqueous solvents, the drug substance is freely soluble to very slightly soluble in DMSO, methanol, and ethanol but is insoluble in *n*-octanol, acetone, and acetonitrile. Imatinib is commercially supplied as 120-capsule bottles containing 100 mg of imatinib free base/capsule. The recommended storage temperature is 25°C.

The originally proposed tradename was Glivec. The FDA Nomenclature Committee determined that this might be confused in oral communication with Glyset, an oral antidiabetes drug. The United States tradename was thus changed to Gleevec.

Toxicology

Preclinical toxicology data included 13-week dog, 6-month rat, and 9-month monkey studies. Most toxicities seen were at doses similar to (or not >2.5 times) the clinical dose calculated according to body surface area. The hematopoietic system, primarily the erythrocytic and myelocytic series, was affected by imatinib administration in the rat, dog, and monkey. Myelosuppression is a direct pharmacological effect of imatinib (14). Lymphoid atrophy and lymphoid depletion were observed in rats and dogs. In the African cynomolgus macaque monkey, treatment with imatinib appeared to increase the recurrence of subclinical malaria. An

Table 1 Phases of CML: Definitions

Chronic phase ^a	
1.	<15% blasts in PB ^b and BM
2.	<30% blasts + promyelocytes in PB or BM
3.	<20% basophils in PB
4.	100×10^9 /Liter platelets
5.	No extramedullary involvement other than spleen or liver
Accelerated phase ^c	
1.	15% to <30% blasts in PB or BM
2.	30% blasts + promyelocytes in PB or BM (but <30% blasts in PB and BM)
3.	20% basophils in PB
4.	< 100×10^9 /Liter platelets
Blast crisis ^d	
1.	30% blasts in PB or BM or
2.	Extramedullary involvement other than spleen or liver

^a All five criteria must be fulfilled.

^b PB, peripheral blood.

^c At least one of the four criteria must be fulfilled.

^d These two evaluations take preference over chronic and accelerated phase results.

explanation for the recrudescence of the malarial infection may be the inhibition of platelet-derived growth factor by imatinib, which is involved in the signaling pathway for induction and expression of inducible nitric oxide synthetase (15). Renal toxicity included hyperplasia of the transitional renal epithelium and the urinary bladder in rats. In the highest dose given to monkeys, focal mineralization and dilation of the renal tubules and tubular nephrosis were observed. Oral but not i.v. dosing of imatinib caused emesis and diarrhea, suggesting a local irritation effect. Hepatic toxicity was seen in the dog after a 2-week course of imatinib. Liver enzymes were elevated, and histological changes included mild multifocal hepatocellular necrosis, single-cell bile duct necrosis, and bile duct hyperplasia. The bile duct hyperplasia persisted after the 4-week recovery period and was associated with peribiliary fibrosis. The testes showed decreased weight and decreased spermatogenesis. Enlarged hemorrhagic ovaries were noted in rats. These findings may be related to the effect of imatinib on c-Kit, a tyrosine kinase implicated in spermatogonial proliferation and ovarian follicle development (16).

In pregnant rats, imatinib was teratogenic, with increased skeletal malformations and anomalies. Teratogenicity in the rabbit has not been observed.

Carcinogenicity studies were not conducted with imatinib. Genotoxicity studies showed imatinib to be clastogenic in the Chinese hamster ovary cell assay, but Ames test and mouse lymphoma assays were negative. Two intermediates in the imatinib manufacturing process, present in small quantities in the final product, were positive for mutagenicity in the Ames test and mouse lymphoma assay.

Clinical Pharmacology

After oral administration to normal volunteers, imatinib was well absorbed (absolute bioavailability of 98%) with peak plasma concentration attained between 2 and 4 h. At clinically relevant concentrations, total binding of imatinib to plasma proteins is ~95%, mostly to albumin and α_1 -acid glycoprotein. The protein binding of the major active metabolite, CGP74588, is unknown. The elimination half-lives of imatinib and

Table 2 Patient characteristics

Patient characteristics	CP (n = 532)	AP (n = 235)	BC (n = 260)
Age			
Median (range)	57.0 (18–90)	56 (22–86)	56 (19–81)
Sex (%)			
Male	311 (58.5)	118 (50.2)	136 (52)
Female	221 (41.5)	117 (49.8)	124 (48)
Race (%)			
Caucasian	463 (87.0)	210 (89.4)	221 (85)
Black	32 (6.0)	10 (4.3)	21 (8)
Other	37 (7.0)	15 (6.3)	18 (7)
Performance status (ECOG ^a)(%)			
0	314 (59.0)	86 (36.6)	42 (16)
1	172 (32.3)	94 (40.0)	108 (42)
2	18 (3.4)	41 (17.4)	97 (37)
3	0	2 (0.9)	3 (1)
Unknown	28 (5.3)	12 (5.1)	10 (4)
Chromosomal abnormalities (%)			
Ph+ only	420 (78.9)	108 (46.0)	94 (36)
Ph+ and other chromosome abnormalities	87 (16.4) ^b	127 (54.0)	166 (64)
Extramedullary disease (%)			
Yes	129 (24.2)	160 (68.1)	178 (68)
No	403 (75.8)	75 (31.9)	82 (32)
Imatinib starting dose (%)			
400 mg/day	524 (98.5)	77 (32.8)	37 (14)
600 mg/day	8 (1.5)	158 (67.2)	223 (86)

^a ECOG = Eastern Cooperative Oncology Group.

^b Twenty-five patients who were Ph+ had missing data regarding other chromosome abnormalities.

CGP74588 from plasma are approximately 18 and 40 h, respectively. Imatinib AUC is dose proportional at the recommended daily dose range of 400 and 600 mg. Approximately 81% of the dose is eliminated within 7 days, 68% in feces and 13% in urine. CGP74588 has *in vitro* potency similar to the parent drug, but its plasma AUC is only 16% of the AUC for imatinib.

Nonlinear mixed effects pharmacokinetic modeling (NONMEM) suggests that body weight and age govern imatinib exposure. For a typical 50-kg patient, the mean oral clearance is 8.5 l/h; for a 100-kg patient, the mean clearance is 11.8 l/h. Even after adjustment for body weight and age, there is considerable unexplained variability in imatinib concentrations. The interpatient variability of clearance is ~40%, and the inpatient variability of the measured plasma concentrations is ~30%.

The NONMEM pharmacokinetic modeling results were used to investigate the relationship between imatinib concentration and treatment response. Neither dose nor steady-state concentration of imatinib predicted the occurrence or time to a hematological or cytogenetic response. A relationship between imatinib steady-state concentration and probability of edema was evident. At steady state, there was also a relationship between age and edema. Patients 60–90 years of age were more likely to develop grade 3 or 4 edema.

CYP3A4 is the major enzyme responsible for imatinib metabolism. A patient on chronic phenytoin therapy (a CYP3A4 inducer), who received 350 mg of imatinib daily, had an AUC_{0-24} about one-fifth of the typical imatinib AUC_{0-24} . When imatinib is coadministered with a single 400-mg dose of ketoconazole, a CYP3A4 inhibitor, AUC_{0-24} increases significantly. Furthermore, imatinib increased the mean C_{max} and AUC of simvastatin, a CYP3A4 substrate. Both imatinib and CGP74588 also appear to be potent *in vitro* CYP2D6 inhibitors.

Pharmacokinetic data are not currently available in pediatric patients. The effect of renal or hepatic impairment on imatinib pharmacokinetics is unknown. Imatinib should be cautiously administered to patients with hepatic function impairment because the drug has a predominant hepatic metabolism and biliary excretion.

Phase I Clinical Studies

A Phase I study evaluated imatinib at doses from 25 to 1000 mg/day in 83 patients with CML progressing on IFN- α treatment (17). Dose-limiting toxicity was not encountered, although a higher frequency of severe toxicities was encountered at imatinib doses >750 mg/day. The most common adverse events were nausea (43%), myalgia (41%), edema (39%), and diarrhea (25%). Common Toxicity Criteria grade 2 or higher elevations of liver enzymes were reported in 7 patients. CHR were reported in 53 of 54 patients receiving a dose \geq 300 mg/day. These patients also had a 31% rate of MCyR and a 13% rate of CCyR (see Table 3 for response criteria). A HR usually occurred within the first treatment month. A cytogenetic response generally required at least 3 months of treatment.

Phase II Clinical Studies

Three open-label, single-arm studies were conducted in patients with Ph+ CML in three clinical settings: CML-CP, CML-AP, and CML-BC. (Definitions of the phases of CML are listed in Table 1.) Imatinib was administered orally once daily with a meal and a large glass of water to decrease gastric irritation. Initially, all patients received 400 mg/day. Early in the study, however, the imatinib dose was increased to 600 mg daily for CML-AP and CML-BC studies. Patients with resistant dis-

Table 3 Efficacy

	CML-CP, IFN failure (n = 532)	CML-AP (n = 235)	CML-BC (n = 260)
Hematologic response ^a	88%	63%	26%
CHR ^b	88%	28%	4%
NEL ^c	NA ^d	11%	3%
RTC ^e	NA	24%	19%
MCyR ^f	49%	21%	13.5%
Complete (confirmed ^g)	30% (16%)	14% (4%)	5% (1%)

^a Hematological responses must be of ≥ 4 weeks duration.

^b CML-BC and CML-AP: absolute neutrophil count $\geq 1.5 \times 10^9$ /liter, platelets $\geq 100 \times 10^9$ /liter, no blood blasts, BM blasts $< 5\%$ and no extramedullary disease. CP: WBC $< 10 \times 10^9$ /liter, platelets $< 450 \times 10^9$ /liter, myelocytes + metamyelocytes $< 5\%$ in blood, no blasts or promyelocytes in blood, basophils $< 20\%$, no extramedullary involvement.

^c CML-BC and CML-AP: same criteria as for CHR but absolute neutrophil count $\geq 1 \times 10^9$ /liter and platelets $\geq 20 \times 10^9$ /liter.

^d NA, not applicable.

^e CML-BC and CML-AP: $< 15\%$ blasts BM and peripheral blood, $< 30\%$ blasts + promyelocytes in BM and peripheral blood, $< 20\%$ basophils in peripheral blood, no extramedullary disease other than spleen and liver.

^f Cytogenetic response criteria: A major response combines both complete and partial responses: complete, 0% Ph+ metaphases; partial, 1–35% Ph+ metaphases.

^g CCyR confirmed by a second BM cytogenetic evaluation performed ≥ 4 weeks after the initial study.

ease or with progressive disease receiving a dose of 400 or 600 mg/day could receive doses of 600 or 800 mg (administered as 400 mg twice daily).

Efficacy

Characteristics of patients enrolled in the three studies are presented in Table 2. Efficacy results are presented in Table 3.

For studies of CML-BC and CML-AP, the primary efficacy variable was the HR rate (CHR), NEL, or RTC. CHR, NEL, and RTC are defined in Table 3. HR had to be confirmed ≥ 4 weeks after the initial response was noted. The secondary efficacy variables were MCyR, time to (and duration of) the above responses, time to progression, and overall survival. For the study of CML-CP, the primary efficacy variable was the MCyR rate. The secondary efficacy variables were HR rate (to be confirmed after ≥ 4 weeks), time to (and duration of) the above responses, time to progression, and overall survival.

In 532 patients with CML-CP, unconfirmed MCyR (single cytogenetic evaluation) was seen in 49%, CCyR in 30%, and CHR in 88%. Three subgroups were defined according to response to prior IFN- α : no CHR within 6 months or loss of CHR (29%, hematological failure); no MCyR within 1 year or loss of MCyR (35%, cytogenetic failure); or IFN intolerance (36%). Unconfirmed MCyRs were observed in 36, 51, and 58% of the three subgroups, respectively. Unconfirmed CCyRs were observed in 20, 30, and 38% of the three subgroups, respectively. The data were not sufficiently mature to estimate response duration for any efficacy endpoints.

In 235 patients with CML-AP, imatinib was dosed starting at 400 mg/day in the first 77 patients and at 600 mg/day in the remaining 158 patients. The rate of HR was 63% (28% CHR).

Median HR duration was estimated to be > 6 months (90% of responders censored for response duration).

The 260 patients with CML-BC included 166 patients (64%) who had chromosome abnormalities in addition to the Ph chromosome. Imatinib was administered starting at 400 mg/day in the initial 37 patients and 600 mg/day in the remaining 223 patients. HR was seen in 26%. Median duration of HR is estimated to be 5.6 months (84% of responders censored for response duration).

Safety

AEs are listed in Table 4. Most patients experienced AEs; they were usually mild to moderate in severity and most frequently included nausea, vomiting, diarrhea, edema, muscle cramps, hemorrhage, musculoskeletal pain, and skin rash.³ AEs were more common in patients with advanced disease (CML-BC $>$ CML-AP $>$ CML-CP), but whether disease status or imatinib dose is the factor responsible for the observed differences is unclear, because most CML-BC and CML-AP patients received imatinib 600 mg/day, whereas CML-CP patients generally received 400 mg/day. At least one severe AE was reported in 36% of patients, although investigators attributed these events to imatinib in only 10%. In the CML-CP study, where the dose was lower (400 mg/day) and disease less advanced, the rate of severe AEs was lower (18%).

Edema was probably the most troubling imatinib side effect; it was most frequently superficial, *e.g.*, periorbital or lower extremity, and it was treated with diuretic therapy or imatinib treatment interruption. More serious forms of fluid retention, occurring in 1–2% of patients, included pleural and pericardial effusions, ascites, and pulmonary edema with or without superficial edema. One patient, with pleural effusion, congestive heart failure, and renal failure, died. The incidence of edema was dose and age related; it was $\sim 20\%$ higher for patients who received imatinib 600 mg/day versus 400 mg/day and for patients > 65 years of age.

Abnormal laboratory findings are presented in Table 5. Hematological cytopenias were more frequent in patients with CML-BC and CML-AP. Median onset of neutropenia was 2 weeks earlier for CML-BC than for the later phases of CML (range, 5–8 weeks). The median duration of neutropenia was 2–4 weeks. Severe hepatic toxicity included grade 3 or 4 transaminase elevation in 1–3% of patients and grade 3 or 4 bilirubin elevation in 0.4–3.5% of patients. Hepatotoxicity usually resolved with imatinib dose reduction or interruption. Permanent imatinib discontinuation for hepatic toxicity was required in 0.5% of patients.

A death from hepatic failure occurred in a patient receiving acetaminophen for chronic fever. At study entry, the patient's liver transaminases and alkaline phosphatase were mildly elevated. Right upper quadrant pain led to detection of severely elevated liver function tests on day 7. Imatinib was discontinued, but the patient died of hepatic failure on day 12. Another patient developed Budd-Chiari syndrome on day 38 of treatment; imatinib was discontinued, and tests normalized. In one case of accidental imatinib overdosage, reversible bilirubin and transaminase elevation occurred after an overdose of 1200 mg/day given for 8 days.

³ Internet address: www.pdr.net.

Table 4 Adverse experiences reported in clinical trials^a

	CML-BC (n = 260)		CML-AP (n = 235)		CML-CP IFN failure (n = 532)	
	600 mg (n = 223)		600 mg (n = 158)		400 mg	
	400 mg (n = 37)		400 mg (n = 77)		(%)	
	All grades	Grade 3/4	All grades	Grade 3/4	All grades	Grade 3/4
Nausea	68	3	68	5	55	2
Fluid retention	67	10	68	6	52	2
Superficial edema	63	5	66	4	51	1
Other fluid retention ^b	16	6	9	3	2	0.6
Muscle cramps	25	0.4	34	0.4	46	0.9
Diarrhea	39	3	49	4	33	0.9
Vomiting	49	3	54	3	28	0.9
Hemorrhage	48	16	35	8	13	0.4
CNS ^c hemorrhage	4	2	1	0.4	0.4	0.2
Gastrointestinal	5	2	3	1	0.2	0
Musculoskeletal pain	37	8	39	7	27	1
Skin rash	32	4	39	4	36	3
Headache	24	4	26	2	28	0.2
Fatigue	24	2	33	3	25	0.2
Arthralgia	21	3	26	5	24	0.8
Dyspepsia	9	0	19	0	18	0
Myalgia	7	0	18	2	18	0.2
Weight increased	4	0.4	6	1	14	2
Pyrexia	38	7	35	7	14	1
Abdominal pain	23	5	26	2	20	0.2
Cough	12	0.8	22	0.9	9	0
Dyspnea	12	4	16	5	5	0.2
Anorexia	10	2	14	1	3	0
Constipation	13	1	13	0.9	4	0
Nasopharyngitis	5	0	10	0	9	0.2
Night sweats	10	0.8	10	1	8	0.2
Pruritus	6	1	10	0.4	9	0.6
Epistaxis	12	3	9	0	3	0
Hypokalemia	12	3	9	1	2	0
Petechiae	10	1	4	0.7	0.9	0
Pneumonia	10	5	7	5	1	0
Weakness	10	3	8	2	5	0.2

^a All adverse events occurring in $\geq 10\%$ of patients are listed regardless of suspected relationship to treatment.

^b Other fluid retention events include pleural effusion, ascites, pulmonary edema, pericardial effusion, anasarca, edema aggravated, and fluid retention not otherwise specified.

^c CNS, central nervous system.

In the three Phase II studies, patient follow-up was generally <1 year, so that long duration safety and efficacy follow-up information is not yet available. As duration of follow-up increases, mechanisms of imatinib resistance may become evident. A possible mechanism of resistance is the reactivation of Bcr-Abl signal transduction as a result of gene mutation or amplification (18).

Regulatory Basis for Approval

The FDA considered two different mechanisms for imatinib NDA approval, regular approval and accelerated approval. Drugs approved for marketing in the United States must be safe and effective. The safety requirement is derived from the Federal Food Drug and Cosmetic Act of 1938. In 1962, the Act was amended to require effectiveness to be demonstrated by adequate and well-controlled investigations. For regular NDA approval, drugs must provide clinical benefit or affect a surrogate end point that is well established as leading to clinical benefit. In 1992, Subpart H was added to the NDA regulations (21 CFR 314) to allow accelerated approval of drugs for diseases that are serious or life-threatening and for which there is no satisfactory alternative therapy. Accelerated approval is based on demonstration of an effect of a drug on a surrogate endpoint that is reasonably likely to predict clinical benefit. After accelerated approval, the applicant is required to perform trial(s) to demonstrate that treatment with the drug is indeed associated with clinical benefit. If the trials fail to demonstrate clinical benefit or if the sponsor does not show "due diligence" in performing the trials, a rapid process for removing the drug from the market may be applied.

As discussed below, the data were deemed sufficient to support accelerated approval in three CML clinical settings.

CML-BC

In CML-BC, accelerated approval was based on HR. The HR rate (26%) with imatinib treatment was comparable with results reported in the literature with cytotoxic drug combinations associated with significant toxicity (4, 19, 20). Imatinib provided an advantage over available therapy for CML-BC by achieving at least a comparable HR rate with less toxicity. Reduction in toxicity is particularly important in the treatment of blast crisis because survival is short, and palliation is the goal of therapy.

Table 5 Laboratory abnormalities in clinical trials

	CML-BC (<i>n</i> = 260)		CML-AP (<i>n</i> = 235)		CML-CP, IFN failure (<i>n</i> = 532)	
	600 mg <i>n</i> = 223 400 mg <i>n</i> = 37 (%)		600 mg <i>n</i> = 158 400 mg <i>n</i> = 77 (%)		400 mg (%)	
	Grade 3	Grade 4	Grade 3	Grade 4	Grade 3	Grade 4
Hematology parameters^a						
Neutropenia	16	46	24	34	25	8
Thrombocytopenia	27	31	30	12	16	<1
Anemia	40	10	31	5	4	<1
Biochemistry parameters^a						
Elevated creatinine	1.2	0	1.3	0	0	0
Elevated bilirubin	3.5	0	1.7	0	0.4	0
Elevated alkaline phosphatase	4.6	0	5.1	0.4	0.2	0
Elevated SGOT (AST)	1.0	0	2.1	0	1.1	0
Elevated SGPT (ALT)	2.3	0.4	3.0	0	1.7	0

^a Common Toxicity Criteria grades. Neutropenia: grade 3, $>0.5-1.0 \times 10^9$ /liter; grade 4, $<0.5 \times 10^9$ /liter). Thrombocytopenia: grade 3, $\geq 10-50 \times 10^9$ /liter; grade 4, $<10 \times 10^9$ /liter. Anemia: hemoglobin, $\geq 65-80$ g/liter; grade 4, <65 g/liter. Elevated creatinine: grade 3, $>3-6$ times the upper limit normal range (ULN); grade 4, >6 times the ULN. Elevated bilirubin: grade 3, $>3-10$ times the ULN; grade 4, >10 times the ULN. Elevated alkaline phosphatase: grade 3, $>5-20$ times the ULN; grade 4, >20 times the ULN. Elevated SGOT or SGPT: grade 3, $>5-20$ times the ULN; grade 4, >20 times the ULN.

CML-AP

For CML-AP, accelerated approval was based on the surrogate endpoints of HR and MCyR. The rates of HR (63%) and MCyR (21%) with imatinib treatment were at least as good as results reported in the literature with available treatments and were achieved with a marked reduction in toxicity. In two studies evaluating toxic multiagent chemotherapy, the HR rates were 25 and 52%, and the rate of MCyR was 8 and 8.5%. Treatment toxicity included neutropenia, infection, diarrhea, and mucositis (4, 20).

CML-CP after Failure of IFN- α

Strong evidence of clinical benefit exists for available treatments for CML-CP. IFN- α 2a recombinant (Roferon-A) was approved by the FDA for treatment of early CML-CP, based on survival benefit demonstrated in a randomized trial conducted by the Italian Cooperative Study Group on CML (IFN- α versus hydroxyurea or busulfan) and supporting evidence from a Phase II trial conducted at M. D. Anderson Cancer Center. Continued IFN- α treatment was not a reasonable option for patients entered in the CML-CP study because patients were intolerant to IFN- α (36%), had CML that progressed during treatment with IFN- α (29%), or had not shown a CHR and/or MCyR after a specified duration of IFN- α treatment (35%). The benefit of additional IFN- α in the last setting has not been studied.

Ordinary drug approval would generally require evidence of enhanced survival in a controlled study comparing imatinib to the best available treatment, probably including longer duration IFN- α treatment in patients who did not achieve a satisfactory response within the protocol specified time interval. Accelerated approval is based on surrogate endpoints, in this setting, MCyR and CCyR. The rates of MCyR (49%) and CCyR (30%) with imatinib treatment were at least as good as results reported with available therapies (21-26), with less toxicity. The imatinib-induced MCyR rate also appeared higher than those in registration trials evaluating IFN- α for treatment of early CML-CP (MCyR rates of 10 and 12%).

Table 6 Response and dose in CML-BC and CML-AP studies

Study	HR		MCyR	
	400 mg	600 mg	400 mg	600 mg
CML-BC	11% (4/37)	29% (64/223)	8% (3/37)	14% (32/223)
CML-AP	63% (48/77)	63% (44/158)	16% (12/77)	24% (38/158)

Dosing

Data from sequential groups of patients with CML-BC and CML-AP treated with an imatinib starting dose of 400 or 600 mg/day suggest a dose-response relationship (Table 6). In exploratory analyses, HR was higher in patients given 600 mg/day than in patients given 400 mg/day in CML-BC, and MCyR was higher in both CML-BC and CML-AP. As discussed previously, sequential data also suggest a relationship between increased dose and an increased incidence of edema in CML-BC and CML-AP. Because CML-CP was only studied at the 400 mg/day dose, data do not exist to examine dose-response or dose-toxicity relationships in this disease phase.

On-Site Inspections

Part of the FDA review process is to inspect manufacturing sites and to audit selected clinical sites. Among the purposes of the clinical audit is to assure that study participants did exist, that they were available for the duration of the study, that they received the assigned study medication, that they had appropriate clinical and laboratory parameters recorded, that they completed the study, and that they had their appropriate outcome recorded. Four study sites were inspected, two in the United States and one each in London, United Kingdom, and Milan, Italy. For the inspections, each case report form was reviewed in detail, and demographic, enrollment physical examination findings, eligibility, efficacy and safety data at follow-up visits, and the laboratory findings (blood tests, BM aspirates, and biopsies) were verified against source documents that included physician progress notes, laboratory reports (hematology,

blood chemistry and BM aspirate, BM biopsy, and cytogenetic), informed consent forms, correspondences with the Institutional Review Board, pharmacy records and drug dispensing cards, and monitoring logs.

The audits disclosed instances of minor deviations from protocol and minor problems with record keeping, serious AE reporting, or drug accountability, which were not of clinical significance. The FDA inspection team recommended that data from all of the subjects at the centers inspected could be used for evaluation of the three protocols in the review of the NDA.

Phase IV Postmarketing Commitments

The letter advising the manufacturer of the approval for marketing (approval letter) of imatinib listed several Phase IV commitments agreed to previously by the NDA applicant. Two of the commitments are intended to demonstrate that imatinib treatment provides clinical benefits, *e.g.*, increased progression-free survival or overall survival (not just an improvement in surrogate endpoints for clinical benefit). The applicant committed to conduct and submit a randomized Phase III study comparing imatinib to IFN- α combined with Cytarabine (1- β -D-arabinofuranosylcytosine) in patients with newly diagnosed CML. The applicant also committed to provide timely follow-up of safety and efficacy data from the studies submitted in the NDA for imatinib treatment of CML-BC, CML-AP, and CML-CP. The approval letter also listed the sponsors' commitment to perform Phase I and Phase II pediatric studies.

Other commitments listed in the approval letter are: implementation of a physician and patient education program regarding the use of concomitant medications with imatinib; evaluation of the pharmacokinetics of imatinib in patients with impaired hepatic function; study of the protein binding of the active metabolites of imatinib; and evaluation of the etiology and treatment of the fluid retention syndrome associated with imatinib treatment.

Conclusion

On the basis of data summarized in this report, imatinib mesylate was approved by the United States FDA for the treatment of CML in three clinical settings: CML-BC, CML-AP, and CML-CP. The entire review process took 72 days, the fastest approval ever for an antineoplastic drug.

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