Sprycel for Chronic Myeloid Leukemia and Philadelphia Chromosome–Positive Acute Lymphoblastic Leukemia Resistant to or Intolerant of Imatinib Mesylate

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Abstract

Purpose: On June 28, 2006, the U.S. Food and Drug Administration approved dasatinib (Sprycel; Bristol-Myers Squibb), a new small-molecule inhibitor of multiple tyrosine kinases, for the treatment of adults with chronic phase, accelerated phase, or myeloid or lymphoid blast phase chronic myeloid leukemia (CML) or Philadelphia chromosome–positive acute lymphoblastic leukemia (Ph^+ ALL) with resistance or intolerance to prior therapy including imatinib. This summary reviews the database supporting this approval.

Experimental Design: Four single-arm multicenter studies supported the efficacy and safety of dasatinib. The primary efficacy end point in chronic phase CML was major cytogenetic response. The primary end point in accelerated phase, myeloid phase, and lymphoid blast phase CML, and Ph^+ ALL was major hematologic response.

Results: The four studies combined enrolled 445 patients. In patients with chronic phase CML, the major cytogenetic response rate was 45% with a complete cytogenetic response rate of 33%. Major hematologic response rates in patients with accelerated phase CML, myeloid CML, lymphoid blast CML, and Ph^+ ALL were 59%, 32%, 31%, and 42%, respectively. Median response durations in chronic phase, accelerated phase, and myeloid phase CML had not been reached. The median durations of major hematologic response were 3.7 months in lymphoid blast CML and 4.8 months in Ph^+ ALL. Common toxicities with dasatinib included myelosuppression, bleeding, and fluid retention.

Conclusions: This report describes the Food and Drug Administration review supporting the approval of dasatinib for CML and Ph^+ ALL based on the rates and durability of cytogenetic and hematologic responses.

Chronic myeloid leukemia (CML) is a clonal disease of the hematopoietic stem cell, characterized by a reciprocal translocation t(9;22)(q34;q11), which forms the Philadelphia chromosome and creates a novel fusion gene *bcr-abl*. CML is diagnosed in ~4,300 patients each year in the United States and accounts for 14% of adult leukemias. The median age at presentation is 45 to 55 years, with a third of patients older than 60 years.

The natural history of CML is progression from an indolent chronic phase in which bone marrow function is preserved, through an accelerated phase characterized by increased numbers of white cells in the peripheral blood, progressive anemia, thrombocytopenia, and increasing splenomegaly, to a rapidly fatal blast phase morphologically indistinguishable from acute leukemia. Median survival is 4 to 6 years, with a range of <1 to >10 years.

Treatment of CML is usually initiated when the diagnosis is established. Until 2001, when imatinib was approved, the two best therapeutic options were allogeneic hematopoietic stem cell transplantation and IFN-α, with or without cytarabine. Hematopoietic stem cell transplantation, the only proven potentially curative treatment, is associated with 15% to 30% treatment-related mortality, and because of demographic/disease characteristics and donor availability, is an option for only about 40% of patients (1, 2). IFN-α induces major cytogenetic responses (MCyR) in 6% to 19% of patients with chronic phase CML (3–5). This rate increases with the addition of cytarabine, (6, 7) and complete cytogenetic responders have longer remission duration and survival compared with nonresponders (8–11). Because there is often a delay before its therapeutic benefit is

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realized, the use of IFN-α is generally limited to chronic phase CML. Due to side effects, many patients tolerate IFN-α poorly.

Imatinib mesylate, an inhibitor of the BCR-ABL tyrosine kinase, received U.S. Food and Drug Administration (FDA) approval in May 2001 (12). Imatinib is most effective in early chronic phase CML, where 95% of patients attain complete hematologic response (CHR) and 85% attain MCyR (13). Imatinib also induces MCyR in 60% of patients with chronic phase CML within 18 months of IFN-α failure (14). In contrast, only 21% and 7% of patients with accelerated phase or blast phase CML achieve MCyR, respectively, (15) and these responses are rarely sustained (16).

Imatinib resistance can be defined as lack of a CHR in patients with chronic phase CML or as a failure to return to chronic phase for patients with CML in accelerated phase or blast phase or Philadelphia chromosome–positive acute lymphoblastic leukemia (Ph^+ ALL; ref 17). The majority of patients with imatinib-resistant CML have secondary *bcr-abl* mutations that either impair the ability of the kinase to adopt the closed conformation to which imatinib binds or directly interfere with drug binding (18–23). Resistance is occasionally caused by BCR-ABL protein overexpression due to *bcr-abl* gene amplification (24) and rarely caused by P-glycoprotein overexpression (25) or α_1-acid glycoprotein interactions (26).

Imatinib resistance is uncommon in patients with early chronic phase CML, whereas its estimated 2-year incidence is 10% to 20% in chronic phase CML post–IFN-α failure, 40% to 50% in accelerated phase CML, and 70% to 80% in blast phase CML or Ph^+ ALL. Risk factors are the presence of cytogenetic clonal evolution and failure to achieve a MCyR (27).

Therapeutic options for patients with imatinib-resistant or refractory CML are limited. Some, particularly those with BCR-ABL overexpression due to gene amplification, respond to increased doses of imatinib. These responses, however, are rarely durable (28, 29). A trial of IFN-α may be feasible for patients with chronic phase CML, but data are limited. In the randomized study of IFN and STI-571 study, only 11 patients who failed first-line therapy with imatinib crossed over to IFN-α plus cytarabine. Three (27%) of these 11 patients attained CHR, and none attained MCyR.

Dasatinib is a small-molecule multikinase inhibitor developed as a treatment for patients with imatinib-resistant CML and Ph^+ ALL. This article summarizes the preclinical and clinical data submitted to the FDA as the New Drug Application for marketing approval for dasatinib.

Chemistry

The chemical name for dasatinib (Fig. 1) is *N*-(2-chloro-6-methylphenyl)-2[6-[4-(2-hydroxylethyl)-1-piperazinyl]-2-methyl-4-pyrimadinlyl]amino]-5-thiazolecarboxamide, monohydrate. Its molecular formula is $C_{22}H_{26}ClN_7O_2S \cdot H_2O$, which corresponds to a formula weight of 506.02 (monohydrate). The anhydrous-free base has a molecular weight of 488.01. Dasatinib is a white to off-white powder and has a melting point of 280°C to 286°C. The drug substance is insoluble in water and slightly soluble in ethanol and methanol. Dasatinib is formulated as tablets in strengths of 20, 50, and 70 mg. Dasatinib tablets have a shelf life of 24 months at room temperature.

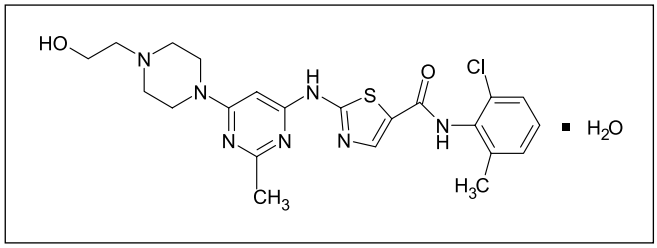

Fig. 1. Structure of dasatinib.

Pharmacology and Toxicology

Dasatinib is a multityrosine kinase inhibitor. It inhibits BCR-ABL, the SRC family of kinases (SRC, LCK, YES, and FYN), c-KIT, EPHA2, and platelet-derived growth factor receptor β at nanomolar concentrations. Dasatinib was active *in vitro* in several imatinib-sensitive or imatinib-resistant leukemic cell lines and inhibited growth of CML and acute lymphoblastic leukemia cell lines overexpressing BCR-ABL.

Acute and chronic toxicities of dasatinib in nonclinical studies included cardiovascular toxicities, electrolyte imbalance, lymphoid depletion, increased triglycerides and cholesterol, increased liver enzymes, increased urinary volume, renal tubular epithelial injury and proteinosis, villus alteration and hemorrhage in the gastrointestinal tract, and reproductive toxicity. Fibrosis and/or mineralization were observed in multiple tissues in repeat-dose studies.

Cardiovascular toxicities associated with dasatinib included QT prolongation *in vitro* and increased systolic, diastolic, and arterial blood pressure in animals. In addition, vascular and cardiac fibrosis, cardiac hypertrophy, myocardial necrosis, hemorrhage of the valves, ventricle, and atrium, and cardiac inflammation were noted in toxicology studies.

In nonclinical studies, several laboratory abnormalities were observed. Decreases in the calcium and phosphorus levels may be, in part, attributed to drug-induced inhibition of bone resorption. *In vitro* studies showed that dasatinib inhibited platelet aggregation in human, monkey, and rat platelet-rich plasma. The hemorrhage noted in animals may be attributed to platelet dysfunction.

Results of repeat-dose toxicity studies indicate the potential for dasatinib to impair reproductive function and fertility. Effects evident in animals included reduced size and secretion of seminal vesicles, immature prostate/seminal vesicles/testis, uterine inflammation and mineralization, cystic ovaries, and ovarian hypertrophy. Dasatinib was teratogenic in rats and rabbits at subtherapeutic exposures. Embryo-fetal toxicities included skeletal malformations, reduced ossification, edema, and microhepatia.

Dasatinib was clastogenic when tested *in vitro* in Chinese hamster ovary cells, with and without metabolic activation. Dasatinib was not mutagenic when tested in *in vitro* bacterial cell assays (Ames test) and was not genotoxic in an *in vivo* rat micronucleus study.

Clinical Pharmacology. The clinical pharmacology of dasatinib was studied in healthy volunteers and in patients with leukemia. The pharmacokinetics in patients did not significantly differ from those in healthy volunteers. No significant effects of patient age or gender on dasatinib pharmacokinetics

were observed. The peak plasma concentrations of dasatinib occur between 0.5 and 6 h after oral dosing. Exposure increased dose proportionally over the dose range of 15 to 240 mg/d, and the mean terminal half-life of dasatinib ranged from 3 to 5 h. Administration of dasatinib with food increased mean exposure by 14%. This increase was not clinically relevant, so dasatinib may be given irrespective of food.

Binding to human plasma proteins *in vitro* was ~96% for dasatinib and 93% for its active metabolite. Dasatinib is extensively distributed in the extravascular space with an apparent volume of distribution of 2,505 liters. After a single oral dose of radio-labeled dasatinib, 85% was recovered in feces (19% as intact parent) and 4% in urine (0.1% as intact parent).

No data are available regarding the influence of hepatic dysfunction on the pharmacokinetics of dasatinib. Evidence suggests that dasatinib is cleared primarily by the liver, so caution should be used when treating patients with hepatic impairment. Because <4% of a single dose is excreted in the urine, clinical studies were not conducted in patients with compromised renal function.

Dasatinib is extensively metabolized primarily by the cytochrome P450 enzyme 3A4, which is responsible for the formation of an active metabolite. Flavin-containing monooxygenase 3 and UDP-glucruonosyltransferase are also involved in the formation of dasatinib metabolites. Exposure to the active metabolite, which is equipotent to dasatinib, is ~5% of the dasatinib exposure.

Because dasatinib is a substrate of CYP3A4, its exposure can be altered by inducers or inhibitors of CYP3A4. Coadministration with the CYP3A4 inducer rifampin decreased dasatinib exposure by ~82%, and coadministration with the potent CYP3A4 inhibitor ketoconazole increased dasatinib exposure 5-fold.

In vitro, dasatinib did not seem to induce human CYP enzymes. Dasatinib is a time-dependant CYP3A4 inhibitor, and can therefore increase exposure of drugs metabolized by CYP3A4. In a study with the CYP3A4 substrate simvastatin, a single 100 mg dose of dasatinib increased the mean exposure of simvastatin by 20%.

Because the solubility of dasatinib is pH dependant, drugs known to alter the pH of the gut can decrease the exposure of dasatinib. Famotidine reduced dasatinib exposure by 61%. As a result, concomitant administration of agents that provide prolonged gastric acid suppression, such as H_2 antagonists and proton pump inhibitors, is not recommended. The use of over-the-counter antacid products is acceptable, providing that the dose of the antacid and dasatinib is separated by at least 2 h.

Exposure-response analyses were done to characterize the relationships between trough levels of dasatinib and effectiveness and incidence of severe toxicity in patients using logistic regression. Data from five phase 2 studies in chronic phase and accelerated phase patients were included, and no significant correlation between C_{trough} of dasatinib and end points of effectiveness and safety could be discerned.

Regulatory Background

Two pathways are available for marketing approval by the FDA of oncology drugs—regular and accelerated. Both regular and accelerated approval require substantial evidence of the effectiveness of the drug from adequate and well-controlled investigations. Adequate and well-controlled investigations are those that include a valid comparison between a test group and a control group and a quantitative assessment of the effects of a drug (30). Guidance promulgated in the 1980s indicated that drug efficacy should be shown by increasing survival, improving the quality of life, or increasing the level of an established surrogate end point for at least one of these outcomes.

In 1992, the Code of Federal Regulations was modified to add a section on Accelerated Approval (Subpart H). This addition allows accelerated approval of drugs for serious or life-threatening diseases if the drug seems to provide a benefit over available therapy and the benefit is determined by the effect of the drugs on a surrogate end point that is reasonably likely to predict clinical benefit. Drugs granted accelerated approval must be studied further by the applicant to verify and describe the relation between the surrogate end point and clinical benefit or between the observed benefit and ultimate outcome. The FDA expects that confirmatory studies to show that treatment with the drug is associated with clinical benefit will usually be under way at the time of accelerated approval (31).

Imatinib mesylate. Imatinib initially received accelerated approval on May 10, 2001, for the treatment of patients with CML in myelin basic protein, accelerated phase, and chronic phase after failure of IFN. This approval was based on hematologic and cytogenetic responses in three nonrandomized, single-arm trials including a total of 1,027 patients with CML (12). Two-year follow-up data from those studies showing high rates of progression-free and overall survival led to the conversion of imatinib from accelerated to regular approval on December 5, 2003.

Dasatinib. The Sponsor submitted an Investigational New Drug application for dasatinib to the FDA on March 11, 2003. On January 5, 2005, the FDA designated dasatinib a Fast Track product, based on responses observed in patients with CML or Ph^+ ALL resistant or intolerant to imatinib. The dasatinib New Drug Application was submitted to the FDA on December 28, 2005.

Overview of Clinical Studies

The Applicant submitted clinical efficacy and safety data from one phase 1 dose-escalation study, four single-arm phase 2 studies, and one randomized phase 2 study evaluating single-agent dasatinib in patients with imatinib-resistant or imatinib-intolerant CML or Ph^+ ALL. Imatinib resistance was defined as failure to achieve a CHR (within 3-6 months) or MCyR (by month 12) or progression of disease after a previous cytogenetic or hematologic response. Imatinib intolerance was defined as imatinib-related toxicity that led to its discontinuation, or inability to tolerate imatinib at 400 mg/d. The presence of specific genetic mutations associated with imatinib resistance was not required for enrollment in any of the studies.

Demonstration of Clinical Efficacy

Phase 1 study. CA180002 was a dasatinib dose-escalation study in 84 patients with any phase of CML or Ph^+ ALL and hematologic resistance or intolerance to imatinib. Of these, 63 were dosed on a twice a day schedule with total daily doses

Table 1. Response rates by disease category in CA180002

Response	CP CML* (n = 19)	AP CML (n = 11)	MB CML (n = 23)	LB CML/Ph$^+$ ALL (n = 10)	Total (N = 63)
MCyR	8 (42%)	3 (27%)	8 (35%)	8 (80%)	27 (43%)
MaHR †	17 (89%)	6 (55%)	7 (30%)	5 (50%)	35 (56%)

Abbreviations: CP, chronic phase; AP, accelerated phase; MB, myeloid; LB, lymphoid blast; MaHR, major hematologic response.
*Twice a day cohorts only.
† CHR.

ranging from 50 to 240 mg, and 21 were dosed once daily, with doses ranging from 15 to 180 mg. Over 40% of all treated patients attained major hematologic and/or cytogenetic responses (Table 1).

Most responses in patients with chronic phase CML occurred among those receiving between 100 and 140 mg daily (or 50 to 70 mg twice a day). In advanced phases of CML and Ph$^+$ ALL, most responses were documented at 50 mg twice a day and 70 mg twice a day (Table 2).

At the time the New Drug Application was submitted, CA180002 was ongoing, with 60% of patients remaining on treatment. Only two patients had National Cancer Institute Common Terminology Criteria adverse events grade 3 or higher during the first 4 weeks of treatment: one chronic phase CML patient had grade 4 thrombocytopenia at 35 mg twice a day, and one myeloid CML patient had grade 3 pleural effusion and grade 4 pericardial effusion at 120 mg twice a day. The maximum tolerated dose was thus not defined, and the phase 2 dose was based on primarily on efficacy rather than safety criteria.

Single-arm phase 2 studies. The Sponsor submitted efficacy data for a total of 445 patients enrolled on four single-arm phase 2 studies. Combined, 49% of patients were women, 89% were White, 10% were Black or Asian, 23% were over the age of 65 years, and 3% were over age 75 years. Most patients had received prior cytotoxic chemotherapy and were imatinib resistant.

All patients received dasatinib 70 mg twice a day continuously. Treatment was interrupted for dasatinib-related grade $\geq$2 nonhematologic toxicity or grade 4 neutropenia after 14 days of treatment (with marrow cellularity <10%) and was discontinued for most grade $\geq$3 treatment–related toxicity. Dose escalation to 100 mg twice a day in the absence of prohibitive toxicity was recommended for patients with (*a*) rising percent blasts on two consecutive hematologic assessments at least 1 week apart, (*b*) no CHR within 1 month of study therapy, (*c*) no complete cytogenetic remission by 3 months of study therapy, or (*d*) loss of response.

The New Drug Application was based on interim results from the ongoing phase 2 studies. All enrolled patients had a minimum of 6 months of follow-up after the start of dasatinib therapy. Median durations of treatment ranged from 5.6 months in patients with chronic phase CML to 2.8 months in patients with lymphoid blast CML.

The primary efficacy end point for chronic phase CML was MCyR, which included complete and partial cytogenetic responses. The primary efficacy end point for accelerated phase, myeloid phase, and lymphoid blast phase CML and Ph$^+$ ALL was major hematologic response, which included CHR and no evidence of leukemia (same as CHR but with incomplete neutrophil and/or platelet recovery).

In patients with chronic phase CML, the MCyR rate was 45% with a complete cytogenetic remission rate of 33%. MCyR rates were 59%, 32%, 31%, and 42% in patients with accelerated phase CML, myeloid CML, lymphoid blast CML, and 42% in Ph$^+$ ALL, respectively (Table 3).

The median durations of hematologic and cytogenetic responses had not been reached in patients with chronic phase, accelerated phase, and myeloid CML. Median durations of major hematologic response were 3.7 months in lymphoid blast CML and 4.8 months in Ph$^+$ ALL. Response rates were higher in imatinib-intolerant than in imatinib-resistant patients with chronic phase CML (data not shown). No age- or gender-related differences were apparent.

Safety

Overview. The safety population included 911 patients who received dasatinib: 565 from the efficacy database plus 346 for whom data were submitted as part of a 3-month safety update while the application was under review. Most patients (>95%) were treated with a starting dose of 70 mg twice a day. The

Table 2. Dasatinib doses required for responses in CA180002 (all treated patients)

Disease	Schedule	n	Dose to achieve MCyR, median (range)	Dose to achieve CHR, median (range)
CP CML	QD	21	105 mg daily (30-180 mg)	105 mg daily (15-180 mg)
CP CML	BID	19	60 mg BID (35-70 mg)	50 mg BID (25-70 mg)
AP CML	BID	11	90 mg BID (50-120 mg)	70 mg BID (50-120 mg)
MB CML	BID	23	70 mg BID (50-90 mg)	70 mg BID (50-70 mg)
LB CML/Ph$^+$ ALL	BID	10	70 mg BID (25-90 mg)	70 mg BID (70-90 mg)

Abbreviations: QD, daily; BID, twice daily.

Table 3. Efficacy of dasatinib in single-arm phase 2 trials

	CP CML (*n* = 186)	AP CML (*n* = 107)	MB CML (*n* = 74)	LB CML (*n* = 42)	Ph$^+$ ALL (*n* = 36)
Hematologic response rate, % (95% CI)*					
MaHR	NA	**59 (49-68)**	**32 (22-44)**	**31 (18-47)**	**42 (26-59)**
CHR	90 (85-94)	33 (24-42)	24 (15-36)	26 (14-42)	31 (16-48)
NEL	NA	26 (18-36)	8 (3-17)	5 (1-16)	11 (3-26)
Cytogenetic response rate, % (95% CI)					
MCyR	**45 (37-52)**	31 (22-41)	30 (20-42)	50 (34-66)	58 (41-74)
CCyR	33 (26-40)	21 (14-30)	27 (17-39)	43 (28-59)	58 (41-74)

NOTE: All calculations were made from the intent-to-treat population. Numbers in bold represent primary end points that were used for approval.
Abbreviations: 95% CI, 95% confidence interval; CCyR, complete cytogenetic remission; NA, not applicable; NEL, no evidence of leukemia.
*Confirmed after at least 4 wks.

median duration of therapy was 6 months (range 0-19); 21% were treated for <3 months, 23% were treated for 3 to 6 months, and 57% were treated for >6 months.

Dose modifications for adverse events. Most patients required at least one dose interruption, dose reduction, or both due to toxicity; relatively few required discontinuation (Table 4). Dose modifications were more common in patients with chronic phase and accelerated phase CML than in those with more advanced disease. Hematologic toxicity was the most common reason for dose adjustment in patients with chronic phase and accelerated phase CML, whereas nonhematologic toxicity was more often the reason in blast-phase disease (data not shown).

Adverse event profile. The most common treatment-emergent adverse events in the pooled safety population were gastrointestinal (e.g., diarrhea, nausea, vomiting, anorexia, and abdominal pain), constitutional (e.g., pyrexia, headache, fatigue, and asthenia), fluid retention, and bleeding events. Table 5 summarizes the treatment-emergent adverse events with incidences of at least 10% in the safety population.

Laboratory events. Myelosuppression was common in all patient populations. Baseline grade 3 or 4 neutropenia and thrombocytopenia were reported in 7% to 31% and 1% to 58% of patients, respectively. These both became more frequent during treatment, especially in patients with advanced disease (Table 6). Most patients experiencing severe myelosuppression recovered after dose interruption and/or reduction; 1% required permanent discontinuation of treatment.

Hypocalcemia was the most common nonhematologic laboratory abnormality, followed by hypophosphatemia, hyponatremia, liver function abnormalities, and elevated creatinine. Most patients had normal serum aminotransferase levels at baseline. Approximately half of patients developed an elevated aspartate aminotransferase, alanine aminotransferase, or both, while on study. Grade 3 or 4 elevations occurred in 1% of patients with chronic phase CML, 2% with accelerated phase CML, 4% with myeloid CML, and 9% with lymphoid blast CML/Ph$^+$ ALL. Grade 3 or 4 hyperbilirubinemia was rare in patients with chronic phase and accelerated phase CML (0% and 2%, respectively) and more common in those with myeloid CML (8%) and lymphoid blast CML/Ph$^+$ ALL (4%). These changes usually resolved over weeks and, in only two cases, required dose interruption or reduction. No patient developed manifestations of liver failure. Most patients developing grade 3 and 4 hepatic toxicity had no recognized precipitating factors.

Grade 3 or 4 hypocalcemia and hypophosphatemia were reported in patients with all phases of CML and most frequently in those with advanced disease. No patient required dose modification due to hypercalcemia, and there were no reports of muscle spasm. Patients developing grade 3 or 4 hypocalcemia often recovered with oral calcium supplementation.

Grade 3 or 4 elevations in creatinine occurred in nine patients (1%) in the safety population. Many of them had prior histories of renal disease or acute illnesses such as infection that seemed to contribute to the development of renal insufficiency.

Bleeding events. Because dasatinib caused platelet dysfunction *in vitro* and thrombocytopenia, patients taking anticoagulants or medications that inhibit platelet function were excluded from the registration studies. Forty percent of the safety population experienced bleeding events of any type, and 10% experienced grade 3 or 4 bleeding. Epistaxis was the most common event, occurring in 11% of patients, followed by gastrointestinal bleeding in 14%. Seven percent experienced grade 3 or 4 gastrointestinal hemorrhage. Six fatal bleeding events—five brain hemorrhages and one pulmonary hemorrhage—were reported.

Fatal brain hemorrhages tended to occur in patients with blast-phase disease in the setting of grade 4 thrombocytopenia.

Table 4. Patients requiring dasatinib dose modification

Disease phase	Dose reduction (%)	Dose interruption (%)	Discontinuation (%)
CP CML	61	82	6
AP CML	53	81	5
MB CML	36	61	11
LB CML/Ph$^+$ ALL	18	39	6

An additional grade 3 subdural hematoma occurred in a Ph^+ ALL patient whose platelet count was 56,000/μL.

Fluid retention events. Half of patients in the dasatinib trials experienced fluid retention, which was grade 3 or 4 in 9%. Pleural effusion was reported in 22% of patients across all studies and was grade 3 or 4 in 5%. Grade 3 or 4 pericardial effusion, pulmonary edema, ascites, and generalized edema were each reported in 1%. Fluid retention occurred in patients at all disease stages and frequently necessitated dose reduction or interruption, diuretics, or short courses of steroids.

Cardiac events. *In vitro* data suggest that dasatinib has the potential to prolong ventricular repolarization. Electrocardiograms were done in all dasatinib studies before treatment, on days 1 and 8 of the first cycle, and at end of treatment. Electrocardiograms were also obtained in the accelerated phase CML, myeloid CML, and lymphoid blast CML/Ph^+ ALL studies after the first and second cycles, and in the chronic phase CML study every 3 months. A pooled analysis of all electrocardiograms showed dasatinib to prolong the QT interval (with Fridericia's correction; ref. 32) an average of 3 to 6 ms (upper 95% confidence interval; ~8 ms). Treatment was infrequently associated with QT interval (with Fridericia's correction; ref. 32) values >500 ms (0.7% of patients) or increases from baseline >60 ms (2.9% of patients). No relation was seen between QTc and cumulative exposure. Two patients had five-beat runs of asymptomatic, nonsustained ventricular tachycardia. No cases of torsade de pointes were reported.

Twenty patients (4%) in the safety population developed congestive heart failure or ventricular dysfunction. Of them, 12 had prior histories of cardiovascular disease. The median time

Table 5. Treatment-emergent adverse events occurring in ≥10% of patients

	All patients (n = 911)		CP CML (n = 488)	AP CML (n = 186)	MB CML (n = 132)	LB CML/Ph^+ ALL (n = 105)
	All grades	Grades 3/4	Grades 3/4	Grades 3/4	Grades 3/4	Grades 3/4
Preferred term	% of patients					
Fluid retention	50	9	6	6	23	9
Superficial edema	36	1	0	2	3	2
Pleural effusion	22	5	3	3	14	8
Other fluid retention	14	5	4	4	12	3
Generalized edema	5	1	<1	0	2	1
Congestive heart failure/cardiac dysfunction	4	2	3	1	5	1
Pericardial effusion	4	1	<1	1	3	0
Pulmonary edema	4	1	1	2	0	1
Ascites	1	1	0	1	2	2
Pulmonary hypertension	1	0	<1	1	2	0
Diarrhea	49	5	3	10	18	6
Headache	40	2	2	2	4	6
Hemorrhage	40	10	3	18	23	17
Gastrointestinal bleeding	14	7	2	12	14	10
Central nervous system bleeding	2	1	0	1	2	2
Musculoskeletal pain	39	4	2	3	6	13
Pyrexia	39	5	1	5	13	9
Fatigue	39	3	2	4	4	8
Skin rash	35	1	1	1	1	4
Nausea	34	1	<1	0	5	2
Dyspnea	32	6	5	7	11	9
Cough	28	<1	<1	1	1	0
Infection (bacterial, viral, fungal, or nonspecified)	34	7	4	8	15	13
Upper respiratory tract infection/inflammation	26	1	1	1	5	1
Abdominal pain	25	2	1	2	4	6
Pain	26	2	<1	1	5	4
Vomiting	22	1	1	2	2	2
Anorexia	19	1	<1	2	2	3
Asthenia	19	3	1	4	6	5
Arthralgia	19	1	1	0	3	2
Mucosal inflammation (mucositis/stomatitis)	16	1	<1	0	4	1
Dizziness	14	<1	<1	0	0	0
Weight decreased	14	1	<1	1	1	0
Constipation	14	<1	<1	0	1	0
Chest pain	13	1	<1	0	4	3
Neuropathy (including peripheral neuropathy)	13	1	1	1	0	0
Myalgia	12	1	0	1	2	2
Abdominal distention	11	0	0	0	0	0
Weight increased	11	1	<1	1	1	1
Arrhythmia	11	2	2	1	2	3
Chills	11	<1	0	1	0	0
Pruritus	11	0	0	0	0	0
Pneumonia (bacterial, viral, or fungal)	11	6	3	8	11	10
Febrile neutropenia	9	8	2	11	17	20

Table 6. Common Terminology Criteria for Adverse Events grades 3 or 4 laboratory abnormalities in clinical studies

	CP CML (*n* = 488)	AP CML (*n* = 186)	MB CML (*n* = 132)	LB CML/Ph$^+$ ALL (*n* = 105)
			% of patients	
Hematology variables				
Neutropenia	49	74	83	81
Thrombocytopenia	48	83	82	83
Anemia	18	70	70	51
Biochemistry variables				
Hypophosphatemia	11	13	23	21
Hypocalcemia	2	9	20	15
Elevated alanine aminotransferase	1	4	7	11
Elevated aspartate aminotransferase	1	2	5	8
Elevated bilirubin	<1	1	5	8
Elevated creatinine	0	2	1	1

from start of study drug to clinical detection of ventricular dysfunction was 19 days (range 3-104).

Discussion

Efficacy findings. Data submitted from five single-arm studies showed dasatinib to induce hematologic and cytogenetic responses in patients with all phases of CML and with Ph$^+$ ALL who were extensively pretreated, imatinib-resistant or imatinib-intolerant, and with otherwise limited treatment options. The randomized trial CA180017 was too small and follow-up was too short to provide useful comparative data.

Most hematologic and cytogenetic responses occurred during the first 3 months of treatment and were relatively durable. Although the follow-up duration in these ongoing studies is still short, nearly all responding patients with chronic phase, accelerated phase, and myeloid CML remained in response at the 6-month data cutoff. Median durations of major hematologic response were 3.7 and 4.8 months in patients with lymphoid blast CML and Ph$^+$ ALL, respectively.

Safety findings. During a 6-month median duration of exposure, the majority of patients experienced adverse events requiring dose reduction or interruption. The most commonly reported adverse events were gastrointestinal and constitutional symptoms and fluid retention. The most common grade 3 or 4 toxicity was myelosuppression, which was generally reversible. Although myelosuppression was more frequent in patients with advanced CML or Ph$^+$ ALL than in those with chronic phase CML, doses were more often modified for chronic phase and accelerated phase CML patients than for blast phase patients. This difference may reflect the investigators' willingness to tolerate more treatment-related myelosupression in patients with advanced disease.

Cardiac failure occurred in 4% of patients, most of whom had preexisting risk factors. Dasatinib prolonged the mean QT interval (with Fridericia's correction) by 3 to 6 ms but was rarely associated with cardiac arrhythmia.

The ability to isolate the causes of adverse events in this application was limited by the presence of multiple, frequently overlapping clinical problems in this patient population, and

Table 7. Postmarketing commitments and requests

Postmarketing commitments

- Submit the compete study report and data from CA180002, a bicenter, dose escalation study to determine the safety, pharmacokinetics, and pharmacodynamics of dasatinib in patients with chronic phase, accelerated phase, or blast phase CML or Ph+ ALL who have hematologic resistance to imatinib.
- Submit the complete study report (24 mo follow-up) and data from CA180005, a phase 2 multicenter study of dasatinib in patients with accelerated phase CML resistant to or intolerant of imatinib.
- Submit the complete study report (24 mo follow-up) and data from CA180006, a phase 2 multicenter study of dasatinib in patients with myeloid CML resistant to or intolerant of imatinib.
- Submit the complete study report (24 mo follow-up) and data from CA180013, a phase 2 multicenter study of dasatinib in patients with chronic phase CML resistant to high-dose imatinib or intolerant of imatinib.
- Submit the complete study report (24 mo follow-up) and data from CA180017, a randomized, open-label multicenter study of dasatinib vs imatinib 800 mg/d in patients with chronic phase CML resistant to imatinib at a dose of 400 to 600 mg/d.
- Submit the complete study report (24 mo follow-up) and data from CA180015, a phase 2 multicenter study of dasatinib in patients with lymphoid blast CML resistant to high-dose imatinib or intolerant of imatinib.

Other postmarketing requests

- Submit the complete study report (24 mo follow-up) and data from CA180034, a randomized, two-by-two, open-label study of dasatinib in patients with chronic phase CML resistant to or intolerant of imatinib.
- Submit the complete study report and data from CA180051, a single-dose pharmacokinetic study of dasatinib in patient with hepatic impairment compared with healthy adult subjects.
- Submit the complete study report and data from CA180021, an open-label, single-sequence study to evaluate the effect of ketoconazole on the pharmacokinetics of dasatinib in patients with advanced solid tumors.

by the fact that nearly all the data were from single-arm trials. Nonetheless, the gastrointestinal toxicities and fluid retention events, as well as myelosuppression and hypocalcemia, seemed to be drug related. It is difficult to ascertain the degrees to which the drug or disease were responsible for the high incidences of bleeding and infection.

Dosing considerations. The Applicant based the dasatinib dose for all phase 2 studies on phase 1 efficacy data. Although responses were observed at lower doses, insufficient data exist to recommend a starting dose other than 70 mg twice a day Accordingly, the FDA recommended that the Applicant study the safety and efficacy of dasatinib at a lower dose.

Concomitant treatments known to induce or inhibit CYP3A4 activity should be avoided. If an alternative treatment is unavailable, a higher dasatinib dose should be considered in the presence of a CYP3A4 inducer, and a lower dose should be considered in the presence of a CYP3A4 inhibitor. CYP3A4 substrates with narrow therapeutic indices should be administered with caution in patients receiving dasatinib.

Marketing approval. The FDA granted dasatinib accelerated approval for the treatment of adults with chronic phase, accelerated phase, or blast phase CML with resistance or intolerance to prior therapy including imatinib. The approval was based on cytogenetic or hematologic responses with limited duration, and was similar to that initially granted for imatinib. Regular approval may be granted when results of completed trials with 24-month follow-up are submitted.

The FDA granted dasatinib regular approval (i.e., not under Subpart H) for the treatment of adults with Ph^+ ALL with resistance or intolerance to prior therapy because durable complete responses in acute leukemia are considered evidence of clinical benefit.

Postmarketing commitments. The dasatinib approval was contingent upon the Applicant's agreeing to six postmarketing or phase 4 commitments. In addition, the Applicant agreed to three postmarketing requests (Table 7).

Acknowledgments

The views expressed are the result of independent work and do not necessarily represent the views and findings of the U.S. FDA.

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