

NDA 21-588-S016-2006-03-27
Executive Summary
Pediatric Ph+ CML

Reviewer Name	Martin H. Cohen, M.D. Shenghui Tang, Ph.D.
Review Completion Date	6/1/06
Established Name	Imatinib mesylate (STI571)
Trade Name	Gleevec
Therapeutic Class	Molecularly targeted drug
Sponsor	Novartis
Priority Designation	S

Formulation

Gleevec[®] (imatinib mesylate) film-coated tablets contain imatinib mesylate equivalent to 100 mg or 400 mg of imatinib free base. of age.

Dosing Regimen

The recommended dose of Gleevec as single-agent for newly diagnosed pediatric patients with Ph+ CML is 340 mg/m²/day. If the child could not swallow the capsule, the capsule contents were dissolved in water or apple juice. There is no experience in dosing children <2 years

The recommended Gleevec dosage is 260 mg/m²/day for children with Ph+ chronic phase CML recurrent after stem cell transplant or who are resistant to interferon-alpha therapy.

The prescribed dose should be administered orally, once-daily, with a meal and a large glass of water.

Gleevec Pediatric Indication(s)

Proposed: Gleevec is indicated as a single agent for the treatment of pediatric patients with newly diagnosed Ph+ CML in chronic phase.

Gleevec is also indicated for the treatment of pediatric patients with Ph+ chronic phase CML whose disease has recurred after stem cell transplant or who are resistant to interferon-alpha therapy. There are no controlled trials in pediatric patients demonstrating a clinical benefit, such as improvement in disease-related symptoms or increased survival.

Executive Summary

The purpose of the present submission is to present data to support the proposed indication: “Gleevec is indicated as a single agent for the treatment of pediatric patients with newly diagnosed Ph+ CML”.

This current sNDA is also intended to meet the terms of the Pediatric Written Request dated 20-Sep-2000 in supporting the above indication and in qualifying for pediatric exclusivity. The application is based on data collected up to 10-Jun-2005 in Study 2108. It also references pediatric data from Study 0103 and Study 03 001 from a previous submission (NDA 21-335/S-003), as well as data from published literature.

Recommendation On Regulatory Action

The clinical reviewer recommends that Gleevec receive accelerated approval for the treatment of pediatric patients with newly diagnosed Ph+ CML. This is based upon the induction of both hematologic and cytogenetic responses in this patient population. A total of 51 pediatric patients with newly diagnosed and untreated chronic phase CML were enrolled in an open-label, multicenter, single arm phase II trial (Study 2108). Patients were treated with Gleevec 340 mg/m²/day. Complete hematologic Response (CHR) was observed in 78% of pediatric patients after 8 weeks of therapy. The complete cytogenetic response (CCyR) rate was 65%, comparable to the results observed in adults. Additionally, partial cytogenetic response (PCyR) was observed in 16%. The majority of patients who achieved a CCyR developed the CCyR between months 3 and 10 with a median time to response of 6.74 months. Estimated survival at 12 months was 98% and estimated survival at 24 months was 84%

In addition, a single-arm Phase I study (0103) enrolled 14 pediatric patients with Ph+ chronic phase CML recurrent after stem cell transplant or resistant to interferon-alpha therapy. Patients were treated at doses of 260 mg/m²/day (n=3), 340 mg/m²/day (n=4), 440 mg/m²/day (n=5) and 570 mg/m²/day (n=2). In the 13 patients for whom cytogenetic data are available, 7 achieved a CCyR, and 4 achieved a PCyR.

In a second Phase I study (03001), 2 of 3 patients with Ph+ chronic phase CML resistant to interferon-alpha therapy achieved a complete cytogenetic response at doses of 242 and 257 mg/m²/day.

Imatinib generally was well tolerated. Grade 3 or 4 toxicities in the 54 pediatric patients of Study 2108 were primarily hematologic. Non-hematological grade 3 or 4 toxicities included allergic reaction/hyper-sensitivity, avascular osteonecrosis and desquamating rash. The incidence of edema/weight gain (14%) remained low, in contrast to the higher incidence rate seen in adult chronic phase patients (59% in study 0106). There were no deaths during the study period and only one patient discontinued study drug due to suspected study drug-related AEs (elevated AST/ALT). Muscle cramps were reported sporadically during the study and there were no episodes of GI hemorrhage. No new safety concerns were raised.

Recommendation On Post-marketing Actions

Continue post-marketing surveillance.

Risk Management Activity

Continue post-marketing surveillance of AE's

Required Phase 4 Commitments

A phase 4 commitment to continue follow-up of pediatric Ph+ CML patients treated in study 2108 to obtain long-duration (5+ years) survival data.

Other Phase 4 Requests

None

Summary Of Clinical Findings

Overview of Clinical Program

This current sNDA is intended to meet the terms of the Written Request dated 20-Sep-2000 to support the indication for treatment of Philadelphia positive (Ph+) CML in pediatric patients and to qualify for pediatric exclusivity. The application is based on data collected up to 10-Jun-2005 in Study 2108. It also includes pediatric data from two phase 1 studies, 0103 and 03 001, from a previous submission (NDA 21-335/S-003), as well as data from published literature.

Efficacy

A total of 51 pediatric patients with newly diagnosed and untreated CML in chronic phase have been enrolled in an open-label, multicenter, single arm phase II trial (Study 2108). Patients were treated with Gleevec 340 mg/m²/day, with no interruptions in the absence of dose limiting toxicity. CHR was observed in 78% of pediatric patients after 8 weeks of therapy. The complete cytogenetic response (CCyR) rate was 65%, comparable to the results observed in adults. Additionally, partial cytogenetic response (PCyR) was observed in 16%. The majority of patients who achieved a CCyR developed the CCyR between months 3 and 10 with a median time to response based on the Kaplan-Meier estimate of 6.74 months.

One open-label, single-arm study (0103) enrolled 14 pediatric patients with Ph+ chronic phase CML recurrent after stem cell transplant or resistant to interferon-alpha therapy. Patients ranged in age from 3-20 years old; 3 were 3-11 years old, 9 were 12-18 years old, and 2 were >18 years old. Patients were treated at doses of 260 mg/m²/day (n=3), 340 mg/m²/day (n=4), 440 mg/m²/day (n=5) and 570 mg/m²/day (n=2). In the 13 patients

for whom cytogenetic data are available, 7 achieved a CCyR, 4 achieved a PCyR and 2 had a minimal cytogenetic response

In a second Phase I study (03001), 2 of 3 patients with Ph+ chronic phase CML resistant to interferon-alpha therapy achieved a complete cytogenetic response at doses of 242 and 257 mg/m²/day.

Safety

Imatinib generally was well tolerated. Grade 3 or 4 toxicities in the 54 pediatric patients of Study 2108 were primarily hematologic. Non-hematological grade 3 or 4 toxicities included allergic reaction/hyper-sensitivity, avascular osteonecrosis and desquamating rash. Of note, the incidence of edema/weight gain (14%) remained low, in contrast to the higher incidence rate seen in adult chronic phase patients (59% in study 0106). There were no deaths during the study period and one patient (731829) discontinued study drug due to suspected study drug-related AEs (elevated AST/ALT). Muscle cramps were reported sporadically during the study and there were no episodes of GI hemorrhage. The incidence of grade 3 or 4 myelosuppression in chronic phase CML patients was higher than has been seen in comparable adult patients. Grade 3 or 4 increases in liver function tests (LFTs) were reported in one patient who was diagnosed with autoimmune hepatitis. No other unusual laboratory findings were reported. Overall, there is concordance with study 2108 and the phase I experience (study 0103) in pediatric patients following treatment with imatinib.

Dosing Regimen and Administration

PK data, available from two early studies, 03 001 and 0103, show that imatinib was rapidly absorbed after oral administration in pediatric patients, with a C_{max} of 2-4 hours. Dosing in children at both 260 mg/m² and 340 mg/m² achieved an AUC similar to the 400 mg and 600 mg daily doses, respectively, in adults. Based on the early findings, the imatinib dose in Study 2108 was selected to be 340 mg/m², and PK/PD analysis confirmed that the 340 mg/m² dose was adequate, with the plasma exposure being similar to that at 600 mg in adults.

Drug-Drug Interactions

CYP3A4 Inhibitors: Substances that inhibit the cytochrome P450 isoenzyme (CYP3A4) activity (e.g., ketoconazole, itraconazole, erythromycin, clarithromycin).may decrease metabolism and increase imatinib concentrations. There is a significant increase in exposure to imatinib (mean C_{max} and AUC increased by 26% and 40%, respectively) when Gleevec is coadministered with ketoconazole (CYP3A4 inhibitor).

CYP3A4 Inducers: Substances that are inducers of CYP3A4 activity may increase metabolism and decrease imatinib plasma concentrations. Co-medications that induce CYP3A4 (e.g., dexamethasone, phenytoin, carbamazepine, rifampin, phenobarbital or St.

John's Wort) may significantly reduce exposure to Gleevec. Pretreatment of healthy volunteers with multiple doses of rifampin followed by a single dose of Gleevec, increased Gleevec oral-dose clearance by 3.8-fold, which significantly ($p < 0.05$) decreased mean C_{max} and $AUC_{(0-\infty)}$. In patients where rifampin or other CYP3A4 inducers are indicated, alternative therapeutic agents with less enzyme induction potential should be considered.

CYP3A4 Substrates: Gleevec increases the mean C_{max} and AUC of simvastatin (CYP3A4 substrate) 2- and 3.5-fold, respectively, suggesting an inhibition of the CYP3A4 by Gleevec. Particular caution is recommended when administering Gleevec with CYP3A4 substrates that have a narrow therapeutic window (e.g., cyclosporine or pimozide). Gleevec will increase plasma concentration of other CYP3A4 metabolized drugs (e.g., triazolo-benzodiazepines, dihydropyridine calcium channel blockers, certain HMG-CoA reductase inhibitors, etc.).

Because warfarin is metabolized by CYP2C9 and CYP3A4, patients who require anticoagulation should receive low-molecular weight or standard heparin.

In vitro, Gleevec inhibits the cytochrome P450 isoenzyme CYP2D6 activity at similar concentrations that affect CYP3A4 activity. Systemic exposure to substrates of CYP2D6 is expected to be increased when coadministered with Gleevec. No specific studies have been performed and caution is recommended.

In vitro, Gleevec inhibits acetaminophen O-glucuronidation (K_i value of 58.5 μM) at therapeutic levels. Systemic exposure to acetaminophen is expected to be increased when coadministered with Gleevec. No specific studies in humans have been performed and caution is recommended.

Enzyme Inhibition: Human liver microsome studies demonstrated that Gleevec is a potent competitive inhibitor of CYP2C9, CYP2D6, and CYP3A4/5 with K_i values of 27, 7.5 and 8 μM , respectively. Gleevec is likely to increase the blood level of drugs that are substrates of CYP2C9, CYP2D6 and CYP3A4/5.

Special Populations

Pediatric patients

Subject of the current review.

Hepatic Insufficiency: The effect of hepatic impairment on the pharmacokinetics of both imatinib and its major metabolite, CGP74588, was assessed in 84 cancer patients with varying degrees of hepatic impairment (**Table 1**) at imatinib doses ranging from 100-800 mg. Exposure to both imatinib and CGP74588 was comparable between each of the mildly and moderately hepatically-impaired groups and the normal group. However, patients with severe hepatic impairment tend to have higher exposure to both imatinib and its metabolite than patients with normal hepatic function. At steady state, the mean C_{max}/dose and AUC_{24}/dose for imatinib increased by about 63% and 45%, respectively, in patients with severe hepatic impairment

compared to patients with normal hepatic function. The mean C_{max}/dose and AUC₂₄/dose for CGP74588 increased by about 56% and 55%, respectively, in patients with severe hepatic impairment compared to patients with normal hepatic function.

Table 1: Liver Function Classification

Liver Function Test	Normal (n=14)	Mild (n=30)	Moderate (n=20)	Severe (n=20)
Total Bilirubin	≤ ULN	1.5 ULN	>1.5-3x ULN	>3-10x ULN
SGOT	≤ ULN	> ULN (can be normal if Total Bilirubin is >ULN)	Any	Any

ULN=upper limit of normal for the institution

Renal Insufficiency: No clinical studies were conducted with Gleevec in patients with decreased renal function (studies excluded patients with serum creatinine concentration more than 2 times the upper limit of the normal range). Imatinib and its metabolites are not significantly excreted via the kidney.

Geriatric Use: In the CML clinical studies, approximately 40% of patients were older than 60 years and 10% were older than 70 years. In the study of patients with newly diagnosed CML, 22% of patients were 60 years of age or older. No difference was observed in the safety profile in patients older than 65 years as compared to younger patients, with the exception of a higher frequency of edema. The efficacy of Gleevec was similar in older and younger patients.

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/s/

Martin Cohen

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