

**CENTER FOR DRUG EVALUATION AND RESEARCH**

**APPROVAL PACKAGE FOR:**

**APPLICATION NUMBER**

**21-588/S-002**

**Medical Review(s)**

# **NDA 21-588 S002**

**Gleevec™, Imatinib Mesylate**

## **Addendum**

**Studies 102 (Blast crisis CML) and 109 (Accelerated Phase CML)**

## **Action**

**Conversion from accelerated approval to regular approval**

**Medical Reviewer**

**Martin H. Cohen, M.D.**

**Medical Team Leader**

**John R. Johnson, M.D.**

**Documents Reviewed**

**Submission NDA 21-335 N-000-  
4M 12-20-02**

## Blast Crisis CML (Study 102)

The study is titled "A phase II open-label study to determine the safety and anti-leukemic effects of ST1571 in patients with Philadelphia chromosome-positive chronic myeloid leukemia in myeloid blast crisis". This study was carried out in the following countries (number of centers): France (3), Germany (5), Italy (5), UK (3), Switzerland (2) and the USA (14). The first patient enrolled on 26 Jul 1999. Data cut-off was 31 Jul 2002

### Objectives:

#### Primary:

- Determination of the rate of hematologic response (confirmed after 4 weeks).

#### Secondary:

- Duration of hematologic response
- Overall survival
- Cytogenetic response
- Safety profile of ST1571
- Improvement in disease-related symptoms.
- Pharmacokinetic (PK) profile in a sub-group of patients.

A total of 260 patients were recruited, of whom 165 had not previously received antineoplastic treatment for advanced CML. The initial Gleevec dose was either 400 mg daily (qd) (pre-amendment 2), or 600 mg qd. (post-amendment 2). Dosage increase from 400 mg qd. to 600 mg qd. and from 600 mg qd. to 400 mg bid (800 mg qd) was permitted in all patients (post-amendment 2) for improved therapeutic effect.

Efficacy results are displayed in the following table.

	400mg n=37	600 mg n=223	Untreated n=165	Pretreated n=95	All patients n=260
Hematologic response	16.2%	33.2%	35.8%	22.1%	30.8%
Complete hematologic response	0	9.4%	9.7%	5.3%	8.1%
No evidence of leukemia	10.8%	3.6%	4.8%	4.2%	4.6%
Return to chronic phase	5.4%	20.2%	21.2%	12.6%	18.1%
Major cytogenetic response	8.1%	16.6%	15.2%	15.8%	15.4%
Complete cytogenetic response	5.4%	7.6%	7.9%	6.3%	7.3%
Partial cytogenetic response	2.7%	9.0%	7.3%	9.5%	8.1%
Overall survival					
Median (months)	4.7	7.1	7.7	4.7	6.9
Estimated 12-month rate	31.7%	32.1%	35.2%	26.6%	32.1%
Estimated 24-month rate	23.0%	17.4%	20.5%	14.5%	18.3%

### Safety

Gleevec was generally well tolerated but relatively frequent reports of CTC grade 3/4 neutropenia and thrombocytopenia were encountered. The most frequently reported AEs included gastrointestinal disturbances, edema, rash and musculoskeletal complaints but these rarely led to discontinuation of therapy.

### Conclusion

These results confirm those of the interim analysis and suggest that ST1571 represents an effective therapeutic agent for the treatment of patients with CML in blast crisis.

## Accelerated Phase CML (Study 109)

The study is titled "A phase II study to determine the safety and anti-leukemic effects of STI571 in adult patients with Philadelphia chromosome positive leukemia including acute lymphoblastic leukemia, acute myeloid leukemia, lymphoid blast crisis chronic myeloid leukemia and accelerated phase chronic myeloid leukemia. A total of 18 centers of which 2 were in France, 4 in Germany, 3 in Italy, 2 in the UK, 1 in Switzerland and 6 in the USA. The first patient enrolled on 9-Aug-1999. Data cut-off was 31-Jul-2002.

### Objectives:

#### Primary

- To determine the rate of hematologic response (HR) lasting  $\geq 4$  weeks in adult patients with Philadelphia chromosome-positive (Ph+) chronic myeloid leukemia (CML) in the accelerated phase (AP).

#### Secondary

- Duration of HR
- Overall survival
- Cytogenetic response (CyR)
- Time to blast crisis
- Improvement of symptomatic parameters,
- Tolerability and safety of STI571 treatment.

Patients enrolled and analyzed for safety and efficacy included 293 patients in total: 235 with CML AP, 48 with relapsed/refractory ALL, 2 with relapsed/refractory AML, and 8 with relapsed/refractory CML in Lymphoid BC. Patients received STI571 400 mg or 600 mg taken orally (po) once a day (qd.). Dose escalation was permitted, to a maximum of 800 mg daily, taken as 400 mg twice daily (bid.).

### Efficacy

Efficacy results are displayed in the following table.

CML AP	400 mg n=77	600 mg n=158	All pts N=235
Hematologic response	64.9%	74.7%	71.5%
Complete hematologic response	33.8%	46.2%	42.1%
No evidence of leukemia	10.4%	13.3%	12.3%
Return to chronic phase	20.8%	15.2%	17.0%
Major cytogenetic response	19.5%	31.0%	27.2%
Complete cytogenetic response	15.6%	22.8%	20.4%
Partial cytogenetic response	3.9%	8.2%	6.8%
Duration of hematologic response			
Median (months)	16.5	28.8	p=0.0035
Estimated 24-month rate still in HR	41.6%	61.0%	
Time to progression			
Median (months)	10.0	22.9	p=0.0026
Estimated 24-month rate without PD	33.5%	49.7%	
Overall survival			
Median (months)	20.9	Not reached	P=0.0088
Estimated 24-month rate alive	46.2%	65.8%	

The median survival in the advanced leukemia population (ALL, AML, LBC) was only 5 months; and only 2 patients are still on treatment.

#### **Safety**

Gleevec was generally well tolerated but relatively frequent reports of CTC grade 3/4 neutropenia and thrombocytopenia were encountered. The most frequently reported AEs included gastrointestinal disturbances, edema, rash and musculoskeletal complaints but these rarely led to discontinuation of therapy.

#### **Conclusion**

These results confirm those of the interim analysis and suggest that ST1571 represents an effective therapeutic agent for the treatment of patients with CML in accelerated phase.

#### **Publications**

Talpaz M, Silver RT, Druker BJ. Imatinib induces durable hematologic and cytogenetic responses in patients with accelerated phase chronic myeloid leukemia: results of a phase 2 study. *Blood* 2002; 99:1928-1937

Ottman OC, Druker BJ, O'Brien SC. A phase 2 study of imatinib in patients with relapsed or refractory Philadelphia chromosome-positive acute lymphoid leukemias. *Blood* 2002; 100:1965-1971.

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John Johnson  
12/4/03 09:33:16 AM  
MEDICAL OFFICER

**CLINICAL REVIEW**

# Clinical Review

<b>Application #</b>	<b>NDA 21-588 S002</b>
<b>Drug Name</b>	<b>Gleevec™, Imatinib mesylate</b>
<b>Medical Reviewer</b>	<b>Martin H. Cohen, M.D.</b>
<b>Medical Team Leader</b>	<b>John R. Johnson, M.D.</b>
<b>Documents reviewed</b>	<b>Submission NDA 21-335 N-000-4M 12-20-02</b>

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# Clinical Review for NDA 21-558 S002

## Executive Summary

Gleevec™ capsule (NDA 21-335) received accelerated approval on May 10, 2001 for the treatment of patients with chronic myeloid leukemia (CML) in blast crisis (BC) (protocol 102), accelerated phase (AP) (protocol 109), or in chronic phase after failure of interferon-alpha therapy (protocol 110). The accelerated approval letter contained two post-marketing commitments. These commitments were later transferred to NDA 21-588 (tablet). The first postmarketing commitment was satisfactorily completed with the submission of final study report for protocol 102 on June 28, 2002. The second postmarketing commitment was satisfactorily completed with the submission of safety and efficacy update on June 27, 2001 and final analysis report on December 20, 2002 for studies 102, 109, and 110.

The present review summarizes data applicable to the conversion of the 2<sup>nd</sup> line CML indication (protocol 110) to full approval status. A revised Gleevec package insert, including updated clinical data from trial 110, is also provided.

532 chronic phase CML patients who had not benefited from prior interferon therapy [failure to achieve (within 6 months), or loss of a complete hematologic response (29%), failure to achieve (within 1 year) or loss of a major cytogenetic response (35%)], or intolerance of prior interferon (36%), were treated at a starting Gleevec dose of 400 mg orally per day; dose escalation to 600 mg was allowed. Patients had received a median of 14 months of prior IFN therapy at doses  $\geq 25 \times 10^6$  IU/week and were all in late chronic phase, with a median time from diagnosis of 32 months. Effectiveness was evaluated on the basis of the rate of hematologic response and by bone marrow exams to assess the rate of major cytogenetic response (up to 35% Ph+ metaphases) or complete cytogenetic response (0% Ph+ metaphases). Median duration of treatment was 29 months with 81% of patients treated for  $\geq 24$  months (maximum = 31.5 months). A complete hematologic response (CHR) was achieved in 95% of patients. The confirmed (second evaluation after  $\geq 4$  weeks) major cytogenetic response rates (MCyR) was 60%. The confirmed complete cytogenetic response (CCyR) rate was 39%.

Favorable treatment responses were sustained. An estimated 87.8% of patients who achieved MCyR maintain their response 2 years after achieving their initial response. After 2 years of treatment, an estimated 85.4% of patients were free of progression to AP or BC, and estimated overall survival was 90.8% [95% CI 88.3, 93.2]. The achievement of MCyR at 3 months was a predictive factor for survival ( $p < 0.001$ ).

## I. Recommendations

### A. Recommendation on Approvability

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The Division of Oncology Drug Products (DODP), Center for Drug Evaluation and Research (CDER), FDA recommends the conversion of the 2<sup>nd</sup> line chronic phase CML indication to full approval status. This recommendation is made because there appears to be clinical benefit, as indicated by sustained cytogenetic remissions in patients who are protocol defined interferon alpha failures (patients had received a median of 14 months of prior IFN therapy at therapeutic dose [ $\geq 25 \times 10^6$  IU/week] and were all in late chronic phase, with a median time from diagnosis of 32 months).

Continued follow-up is still required to determine five-year survival.

### B. Recommendation on Phase 4 Studies and/or Risk Management Steps

None.

## II. Summary of Clinical Findings

### A. Brief Overview of Clinical Program

The title of the study is "A phase II study to determine the efficacy and safety of Gleevec in patients with chronic myeloid leukemia who are refractory to or intolerant of interferon-alpha". A total of 28 centers, 3 in France, 4 in Germany, 7 in Italy, 1 in Switzerland, 3 in the United Kingdom and 10 in the United States participated. The first patient enrolled on 6-Dec-1999. Data cut-off was 31-Jul-2002

The primary objective was to determine the rate of complete (CCyR) and major (MCyR) cytogenetic response to Gleevec. Secondary objectives were to determine the rate and duration of complete hematologic response (CHR) and the duration of CCyR and MCyR; to evaluate the safety profile of Gleevec; to assess improvement in symptomatic parameters; to measure the time to accelerated phase (AP) disease (or blast crisis, BC) and overall survival; to evaluate the rate and the duration of hematologic and cytogenetic response in patients intolerant of IFN; and to evaluate the population pharmacokinetics (PK) of Gleevec.

### B. Efficacy

Median duration of treatment was 29 months with 81% of patients treated for  $\geq 24$  months (maximum = 31.5 months). A complete hematologic response (CHR) was achieved in 95% of patients. The confirmed (second evaluation after  $\geq 4$  weeks) major cytogenetic response rate (MCyR) was 60%. The confirmed complete cytogenetic response (CCyR) rate was 39%.

Favorable treatment responses were sustained. An estimated 87.8% of patients who achieved MCyR maintain their response 2 years after achieving their initial response. After 2 years of treatment, an estimated 85.4% of patients were free of progression to AP or BC, and estimated overall survival was 90.8% [95% CI 88.3, 93.2]. The achievement of MCyR at 3 months was a predictive factor for survival ( $p < 0.001$ ).

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### C. Safety

Safety testing was adequate. The most commonly reported AEs were fluid retention, nausea and muscle cramps. During the course of the study almost all the patients experienced AEs and more than half of them experienced at least 1 grade 3 or 4 event. However, AEs other than those associated with disease progression which led to premature discontinuation of therapy with the study drug were relatively uncommon. The most frequently reported hematological disorders were reports of CTC grade 3 or 4 neutropenia or thrombocytopenia and grade 3 lymphocytopenia. See this review and the current Gleevec label for complete information on safety.

### D. Dosing

Gleevec was supplied as 100 mg capsules. Patients received 400 mg Gleevec orally (p.o.) once daily. Doses could be escalated to 600 mg daily or to 400 mg twice daily for individuals who had an unsatisfactory response to a lower Gleevec dose.

### E. Special Populations

#### 1. Pediatrics

Gleevec has received accelerated approval for chronic phase CML recurrent after stem cell transplant or resistant to IFN-alpha. That open-label, single arm study enrolled 14 pediatric patients with Ph+ chronic phase CML recurrent after stem cell transplant or resistant to alpha interferon therapy. Patients ranged in age from 3 to 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/m<sup>2</sup>/day (n=3), 340 mg/m<sup>2</sup>/day (n=4), 440 mg/m<sup>2</sup>/day (n=5) and 570 mg/m<sup>2</sup>/day (n=2). In the 13 patients for whom cytogenetic data are available, 4 achieved a major cytogenetic response, 7 achieved a complete cytogenetic response, and 2 had minimal cytogenetic response. At the recommended dose of 260 mg/m<sup>2</sup>/day, 2 of 3 patients achieved a complete cytogenetic response. Cytogenetic response rate was similar at all dose levels.

In a second study, 2 of 3 patients with Ph+ chronic phase CML resistant to alpha interferon achieved a complete cytogenetic response at doses of 242 and 257 mg/m<sup>2</sup>/day.

#### 2. Elderly

In the CML clinical studies, approximately 40% of patients were older than 60 years and 10% were older than 70 years. The efficacy of Gleevec was similar in older and younger patients. 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.

#### 3. Renal or Hepatic Impairment

Gleevec and its metabolites are not excreted via the kidney to any significant extent. No specific studies have been performed in patients with impaired renal function. Exposure to

## CLINICAL REVIEW

Gleevec may be expected to be increased if liver function is impaired. A PK study in patients with liver impairment is underway.

#### 4. Gender

There is no effect of gender on the kinetics of Gleevec.

#### 5. Ethnicity

The large majority of study patients are Caucasian. There is insufficient information for other patient populations.

#### 6. Pregnancy

Gleevec should not be used in pregnant females. The drug is currently labeled as class D due to its teratogenic effects in rats and rat fetal loss after post implantation exposure to doses of 60 mg/kg.

### Clinical Review

#### I. Introduction and Background

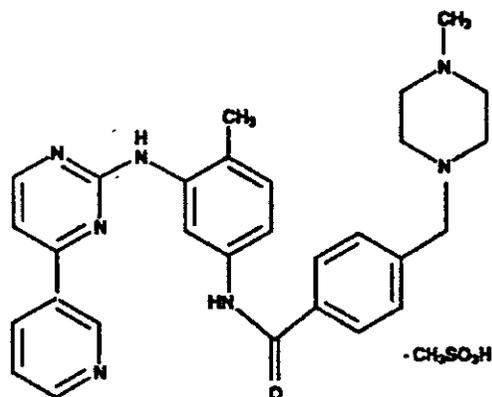
##### A. Drug Established and Proposed Trade Name, Drug Class, Sponsor's Proposed Indication(s), Dose, Regimens, Age Groups

Established Name: **Imatinib mesylate**  
Proprietary Name: **Gleevec™**  
Applicant: **Novartis**  
Drug Class: **Protein-tyrosine kinase inhibitor**

Gleevec™ capsules contain equivalent to 100 mg of imatinib free base. Imatinib mesylate is designated chemically as 4-[(4-Methyl-1-piperazinyl) methyl]-N-[4-methyl-3-[4-(3-pyridinyl)-2-pyrimidinyl]amino]-phenyl]benzamide methanesulfonate. Its molecular formula is  $C_{29}H_{31}N_7O \cdot CH_4SO_3$ . Its structural formula is

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### Indication:

#### Current:

Gleevec is also indicated for the treatment of patients with Philadelphia chromosome positive chronic myeloid leukemia (CML) in chronic phase after failure of interferon-alpha therapy. There are no controlled trials demonstrating a clinical benefit, such as improvement in disease-related symptoms or increased survival in patients with CML chronic phase after failure of alpha interferon.

#### Proposed:

Gleevec is also indicated for the treatment of patients with Philadelphia chromosome positive chronic myeloid leukemia (CML) in blast crisis, accelerated phase, or in chronic phase after failure of interferon-alpha therapy. Gleevec is also indicated for the treatment of pediatric patients with Ph<sup>+</sup> 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.

### Dosage and Administration

#### Current Label:

The recommended dosage of Gleevec™ (imatinib mesylate) is 400 mg/day for adult patients in chronic phase CML. The prescribed dose should be administered orally, with a meal and a large glass of water. Doses of 400 mg or 600 mg should be administered once daily, whereas a dose of 800 mg should be administered as 400 mg twice a day.

In adult patients with chronic phase CML, a dose increase from 400 mg to 600 mg disease, or from 600 mg to 800 mg (given as 400 mg twice daily) may be considered in the absence of severe adverse drug reaction and severe non-leukemia related neutropenia or thrombocytopenia in the following circumstances: disease progression (at any time); failure to achieve a satisfactory hematologic response after at least 3 months of treatment; failure to achieve a cytogenetic response after 6-12 months of treatment; loss of a previously achieved

## CLINICAL REVIEW

hematologic or cytogenetic response. Dosage of Gleevec should be increased by at least 50%, and clinical response should be carefully monitored, in patients receiving Gleevec with a potent CYP3A4 inducer such as rifampin or phenytoin.

Gleevec™ treatment may be continued as long as there is no evidence of progressive disease or unacceptable toxicity.

### Proposed Label:

The recommended dosage of Gleevec® (imatinib mesylate) is 400 mg/day for adult patients in chronic phase CML and 600 mg/day for adult patients in accelerated phase or blast crisis. The recommended Gleevec dosage is 260 mg/m<sup>2</sup>/day for children with Ph+ chronic phase CML recurrent after stem cell transplant or who are resistant to interferon alpha therapy. The recommended dosage of Gleevec is 400 mg/day or 600 mg/day for adult patients with unresectable and/or metastatic, malignant GIST.

The prescribed dose should be administered orally, with a meal and a large glass of water. Doses of 400 mg or 600 mg should be administered once daily, whereas a dose of 800 mg should be administered as 400 mg twice a day.

In CML, a dose increase from 400 mg to 600 mg in adult patients with chronic phase disease, or from 600 mg to 800 mg (given as 400 mg twice daily) in adult patients in accelerated phase or blast crisis may be considered in the absence of severe adverse drug reaction and severe non-leukemia related neutropenia or thrombocytopenia in the following circumstances: disease progression (at any time); failure to achieve a satisfactory hematologic response after at least 3 months of treatment; failure to achieve a cytogenetic response after 6-12 months of treatment; or loss of a previously achieved hematologic or cytogenetic response. In children with chronic phase CML, daily doses can be increased under circumstances similar to those leading to an increase in adult chronic phase disease, from 260 mg/m<sup>2</sup>/day to 340 mg/m<sup>2</sup>/day, as clinically indicated.

Dosage of Gleevec should be increased by at least 50%, and clinical response should be carefully monitored, in patients receiving Gleevec with a potent CYP3A4 inducer such as rifampin or phenytoin.

### B. State of Armamentarium for Indication(s)

Interferon alpha  
Interferon alpha/cytosine arabinoside  
Hydroxyurea  
Busulfan

### C. Important Milestones in Product Development

See Medical Officer Review of NDA 21-335; April 20, 2001, pages 4-15.

## CLINICAL REVIEW

### D. Other Relevant Information

None

### E. Important Issues with Pharmacologically Related Agents

**CYP3A4 Inhibitors:** There was a significant increase in exposure to imatinib (mean  $C_{max}$  and AUC increased by 26% and 40%, respectively) in healthy subjects when Gleevec was co-administered with a single dose of ketoconazole (a CYP3A4 inhibitor).

**CYP3A4 Substrates:** Gleevec increased the mean  $C_{max}$  and AUC of simvastatin (CYP3A4 substrate) by 2- and 3.5-fold, respectively, indicating an inhibition of CYP3A4 by Gleevec.

**CYP3A4 Inducers:** Pretreatment of 14 healthy volunteers with multiple doses of rifampin, 600 mg daily for 8 days, followed by a single 400 mg dose of Gleevec, increased Gleevec oral-dose clearance by 3.8-fold (90% confidence interval = 3.5- to 4.3-fold), which represents mean decreases in  $C_{max}$ ,  $AUC_{(0-24)}$  and  $AUC_{(0-\infty)}$  by 54%, 68% and 74%, of the respective values without rifampin treatment.

**In Vitro Studies of CYP 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  $\mu$ M, respectively. Gleevec is likely to increase the blood level of drugs that are substrates of CYP2C9, CYP2D6 and CYP3A4/5.

## II. Clinically Relevant Findings From Chemistry, Animal Pharmacology and Toxicology, Microbiology, Biopharmaceutics, Statistics and/or Other Consultant Reviews

### A. Clinical Pharmacology and Biopharmaceutics

No clinical pharmacology and biopharmaceutics review was conducted for this supplemental NDA as there was no new data submitted.

### B. Statistics

No new statistics review was conducted for this supplemental NDA.

### C. Chemistry

No CMC review was conducted for this supplemental NDA as there was no new data submitted.

### D. Animal Pharmacology and Toxicology

## CLINICAL REVIEW

No animal pharmacology and toxicology review was conducted for this supplemental NDA as there was no new data submitted.

### III. Human Pharmacokinetics and Pharmacodynamics

#### A. Pharmacokinetics

No human pharmacokinetics and pharmacodynamics review was conducted for this supplemental NDA as there was no new data submitted.

##### *Hepatic and Renal Impairment:*

Gleevec and its metabolites are not excreted via the kidney to any significant extent. No specific studies have been performed in patients with impaired renal function. Exposure to Gleevec may be expected to be increased if liver function is impaired. A PK study in patients with liver impairment is underway.

##### *Special Populations:*

Gender: There is no effect of gender on the kinetics of Gleevec.

Ethnicity: The large majority of study patients are Caucasian. There is insufficient information for other patient populations.

Pregnancy: Gleevec should not be used in pregnant females. The drug is currently labeled as class D due to its teratogenic effects in rats and rat fetal loss after post implantation exposure to doses of 60 mg/kg.

#### B. Pharmacodynamics

No human pharmacodynamics review was conducted for this supplemental NDA as there was no new data submitted.

### IV. Description of Clinical Data and Sources

#### A. Overall Data

A single open label phase II study to determine the efficacy and safety of Gleevec in patients with CML who were refractory to or intolerant of interferon-alpha was performed. A total of 28 centers, 3 in France, 4 in Germany, 7 in Italy, 1 in Switzerland, 3 in the United Kingdom and 10 in the United States participated. The first patient enrolled on 6-Dec-1999. Data cut-off was 31-Jul-2002.

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### **B. Postmarketing Experience**

Postmarketing data is available. See current label.

### **C. Literature Review**

Kantarjian H, Sawyers C, Hochhaus A, et al. Hematologic and cytogenetic responses to imatinib mesylate in chronic myelogenous leukemia. *N Engl J Med* 2002;346: 645 - 652.

## **V. Clinical Review Methods**

### **A. How the Review was Conducted**

The final study report, submitted by the sponsor was reviewed. The primary purpose of the review was to evaluate long-duration follow-up. Hematologic and cytogenetic response rates were evaluated in the initial review.

### **B. Overview of Materials Consulted in Review**

The efficacy and safety review is based on data from Submission NDA 21-335 N-000-4M 12-20-02

### **C. Overview of Methods Used to Evaluate Data Quality and Integrity**

No audit was conducted.

### **D. Were Trials Conducted in Accordance with Accepted Ethical Standards**

Yes

### **E. Evaluation of Financial Disclosure**

The sponsor has submitted certification that there has been no financial arrangement with any of its clinical investigators who participated in study 0110.

## **VI. Integrated Review of Efficacy**

### **A. Brief Statement of Conclusions**

Results are from an updated analysis made after a median duration of treatment of 29 months. Eighty-one percent of patients were treated for  $\geq 24$  months (maximum = 31.5 months). A complete hematologic response (CHR) was achieved in 95% of patients. The confirmed (second evaluation after  $\geq 4$  weeks) major cytogenetic response rates (MCyR) was 60%. The confirmed complete cytogenetic response (CCyR) rate was 39%.

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The median time to hematologic response was 1 month. With a median time from diagnosis of 32 months, an estimated 87.8% of patients who achieved MCyR maintain their response 2 years after achieving their initial response. After 2 years of treatment, an estimated 85.4% of patients were free of progression to AP or BC, and estimated overall survival was 90.8% [88.3, 93.2].

### B. General Approach to Review of the Efficacy of the Drug

The clinical study report dated 13 December 2002 was reviewed.

### C. Detailed Review of Trials by Indication

The efficacy review is based on one multicenter trial.

### D. Protocol Review

#### Objectives

**Primary:** To determine the rate of complete (CCyR) and major (MCyR) cytogenetic response to Gleevec as demonstrated by a decrease in the percentage of Philadelphia chromosome positive (Ph+) cells in the bone marrow (BM), for patients with CML who were hematologically or cytogenetically refractory to, or intolerant of interferon-alpha (IFN).

**Secondary:** To determine the rate and duration of complete hematologic response (CHR) and the duration of CCyR and MCyR; to evaluate the safety profile of Gleevec; to assess improvement in symptomatic parameters; to measure the time to accelerated phase (AP) disease (or blast crisis, BC) and overall survival; to evaluate the rate and the duration of hematologic and cytogenetic response in patients intolerant of IFN; and to evaluate the population pharmacokinetics (PK) of Gleevec.

#### Eligibility Criteria

#### Inclusion Criteria

- Consenting males or females  $\geq 18$  years of age with Ph+ CML.
- With a documented failure of IFN or an IFN-containing therapy, characterized as resistance or refractoriness defined as any of the following:

**Hematologic Resistance** - Failure to achieve a CHR, lasting for at least 1 month despite 6 or more months of IFN or an IFN-containing regimen, in which IFN was administered at a dose of at least 25 million international units (MIU) per week. During this treatment period the cumulative duration of hydroxyurea therapy may not have exceeded 50% of the treatment period with the IFN-containing regimen.

**Cytogenetic Resistance** - Bone marrow cytogenetics showing  $>65\%$  Ph+ after one year of IFN-based therapy,

## CLINICAL REVIEW

**Cytogenetic Refractoriness** - An increase in the Ph<sup>+</sup> chromosome in BM cells by at least 30 percentage points (e.g. from 20% to 50%, or from 30% to 60%) confirmed by two samples at least 1 month apart, or an absolute increase to >65%,

**Hematologic Refractoriness** - A rising WBC count (to a level >20 x 10<sup>9</sup>/L confirmed by two samples taken at least two weeks apart) for patients achieving a complete hematologic response while receiving IFN or an IFN-containing regimen. This regimen must have included IFN at a dose of at least 25 MIU administered per week. During this treatment period the cumulative duration of hydroxyurea therapy may not have exceeded 50% of the treatment period with the IFN-containing regimen.

- With a documented intolerance to IFN therapy defined as a >Grade 3 non-hematologic toxicity persisting for at least one month, for patients receiving IFN or an IFN-containing regimen. IFN was to be administered at a dose of at least 25 MIU/week. Patients who were intolerant of IFN were to have been diagnosed  $\geq$  6 months prior to the time of entry into the study.

### Exclusion Criteria

- Females of childbearing potential without a negative pregnancy test prior to the initiation of study drug. Barrier contraceptive precautions were to be used throughout the trial in both sexes.
- With serum bilirubin and/or SGOT and SGPT and/or creatinine concentrations more than twice the upper limit of the normal range (ULN)
- With > 15% of blasts or basophils in PB or BM
- With  $\geq$  30% of blasts plus promyelocytes in PB or BM With a platelet count of <100 x 10<sup>9</sup>/L
- With an ECOG Performance Status Score  $\geq$  3
- Receiving busulfan within 6 weeks of Day 1
- Receiving treatment with IFN or cytosine arabinoside (Ara-C) within 14 days of Day 1
- Receiving treatment with hydroxyurea within 7 days of Day 1
- Receiving other investigational agents within 28 days of Day 1
- With prior marrow or stem cell transplantation

### Removal of Patients from Therapy or Assessment

- 1) withdrawal of consent
- 2) adverse experience or side effect
- 3) severe concurrent illness
- 4) request of the sponsor
- 5) noncompliance with the protocol
- 6) disease progression warranting alternative treatments/protocols

### Treatment Plan

## CLINICAL REVIEW

Study patients received Gleevec at a dose of 400 mg daily for up to 12 months. Patients completing 12 months of therapy were eligible to continue treatment in the Extension Phase of the study provided that, in the opinion of the investigator, they had benefited from treatment with Gleevec and there were no safety concerns. All patients are to be followed for survival for up to 5 years. Study design is indicated in Table 1.

**Table 1 Study design**

Screening	Core Treatment Phase					End of Phase
Week -1	Month 1-3		Month 4-6		Month 7-13	
Screening Day -7 to 0 Visit 1	Baseline Day 1 Visit 2	Weekly visits Week 1-12 Visits 3-13	Visits every 2 weeks Week 13-24 Visits 14-19		Visits every 6 weeks Week 25-48 Visits 20-23	
					Day 337 Week 49 Visit 24	

Justification for a non-randomized trial in the CML populations included and defined in this trial is based on the poor prognosis of protocol eligible patients and on the lack of a generally accepted standard medical care. The 400 mg daily dose was chosen because it achieved blood levels that have been associated with efficacy.

### Safety Considerations

Reasons for Gleevec dose interruptions and reductions are described below by type of toxicity.

#### Non-hematologic toxicity

In cases of Grade 2 non-hematologic toxicity that did not resolve, study drug was withheld until the toxicity resolved to  $\leq$ Grade 1. Study drug was then resumed at a dose of 400 mg daily. If the Grade 2 toxicity recurred, study drug was withheld until the toxicity resolved to  $\leq$ Grade 1 and the dose was reduced to 300 mg daily.

In cases of Grade 3 or 4 non-hematologic toxicity, study drug was withheld until the toxicity resolved to  $\leq$ Grade 1. Study drug could then be continued at a reduced dose of 300 mg daily.

#### Hematologic toxicity

No dose interruptions or reductions were prescribed for Grade 1 or 2 hematologic toxicity. In cases of Grade 3 or 4 hematologic toxicity, defined as an ANC  $<1000/\text{mm}^3$ , or a platelet count  $<50 \times 10^9/\text{L}$ , study drug was withheld until the toxicity had resolved to  $<$ Grade 2. ANC took precedence over a WBC count in determining the degree of neutropenia (doses not to be interrupted for a patient with a WBC  $<2.0 \times 10^9/\text{L}$  but ANC  $>1000/\text{mm}^3$ ). If the toxicity resolved within two weeks, treatment may have been resumed at a dose of 400 mg daily. If the Grade 3/4 toxicity recurred or persisted for longer than two weeks, study drug was withheld and reduced to 300 mg daily once toxicity had resolved to  $\leq$  Grade 2.

## CLINICAL REVIEW

Patients developing anemia could receive blood transfusion at the discretion of the investigator.

A complete medical history (relevant medical history, prior antineoplastic treatment, disease history, cancer related symptoms, prior concomitant medications) and physical examination was planned

### Laboratory Studies

See Table 2

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**CLINICAL REVIEW**

**Table 2 Evaluation and visit schedule**

	Screening		Month 1					2					3					4					5					6					7					8					9					10					11					12					13																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																									
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222	1223	1224	1225	1226	1227	1228	1229	1230	1231	1232	1233	1234	1235	1236	1237	1238	1239	1240	1241	1242	1243	1244	1245	1246	1247	1248	1249	1250	1251	1252	1253	1254	1255	1256	1257	1258	1259	1260	1261	1262	1263	1264	1265	1266	1267	1268	1269	1270	1271	1272	1273	1274	1275	1276	1277	1278	1279	1280	1281	1282	1283	1284	1285	1286	1287	1288	1289	1290	1291	1292	1293	1294	1295	1296	1297	1298	1299	1300	1301	1302	1303	1304	1305	1306	1307	1308	1309	1310	1311	1312	1313	1314	1315	1316	1317	1318	1319	1320	1321	1322	1323	1324	1325	1326	1327	1328	1329	1330	1331	1332	1333	1334	1335	1336	1337	1338	1339	1340	1341	1342	1343	1344	1345	1346	1347	1348	1349	1350	1351	1352	1353	1354	1355	1356	1357	1358	1359	1360	1361	1362	1363	1364	1365	1366	1367	1368	1369	1370	1371	1372	1373	1374	1375	1376	1377	1378	1379	1380	1381	1382	1383	1384	1385	1386	1387	1388	1389	1390	1391	1392	1393	1394	1395	1396	1397	1398	1399	1400	1401	1402	1403	1404	1405	1406	1407	1408	1409	1410	1411	1412	1413	1414	1415	1416	1417	1418	1419	1420	1421	1422	1423	1424	1425	1426	1427	1428	1429	1430	1431	1432	1433	1434	1435	1436	1437	1438	1439	1440	1441	1442	1443	1444	1445	1446	1447	1448	1449	1450	1451	1452	1453	1454	1455	1456	1457	1458	1459	1460	1461	1462	1463	1464

## CLINICAL REVIEW

### Pharmacodynamic Assessments

No human pharmacodynamics review was conducted for this supplemental NDA as there was no new data submitted.

### Response Evaluation

#### Complete hematologic response (CHR) Study 0110

WBC  $< 10 \times 10^9/L$   
Myelocytes + metamyelocytes  $< 5\%$  in PB  
No blasts + promyelocytes in PB  
 $< 20\%$  basophils in PB  
No extramedullary involvement

#### Cytogenetic response

Based on % positive cells = (positive cells / examined cells) x 100, at each bone marrow assessment the cytogenetic response was either:

- Complete: 0% Ph+ cells
- Partial:  $> 0 - 35\%$  Ph+ cells
- Minor:  $> 35 - 65\%$  Ph+ cells
- Minimal:  $> 65 - 95\%$  Ph+ cells
- None:  $> 95\%$  Ph+ cells
- Not done:  $< 20$  metaphases were examined and/or response could not be assigned

A bone marrow sample was to be considered as assessable for cytogenetic response only if it contained  $\geq 20$  metaphases. This condition was always maintained for affirmation of complete response. However, an assessment of partial response was retained in a sample with  $< 20$  metaphases when it was immediately preceded or followed by a complete or partial response in another sample. A confirmed cytogenetic response required that response be present in 2 consecutive bone marrow exams.

#### Duration of major cytogenetic response-

This duration was evaluated for all patients with major cytogenetic response and was defined as the time between first documented complete or partial response and the earliest of the following:

- loss of complete cytogenetic response- increase to  $> 0\%$  Ph+ cells.
- loss of partial cytogenetic response -increase by  $\geq 30\%$  Ph+ cells compared to lowest value before current assessment or an increase to  $\geq 65\%$  Ph+ cells
- discontinuation due to unsatisfactory therapeutic effect or death.

## CLINICAL REVIEW

Patients still on study at the date of cut-off were censored at the time of their last bone marrow evaluation for cytogenetics, as long as there was no evidence of loss of major cytogenetic response. Patients discontinuing were censored at the time of the last bone marrow evaluation if the discontinuation was for reasons other than unsatisfactory therapeutic effect or death.

### **Time to complete or major cytogenetic response-**

Time to cytogenetic response was defined for all patients with complete or major cytogenetic response as the time until first documented complete (or major) cytogenetic response.

Time to event analyses have been made in which duration = (end date - start date) + 1. If not mentioned otherwise, durations were censored at the last examination date, when patients were still on study without evidence of progression (and/or loss of response) or patients discontinued due to reasons other than unsatisfactory therapeutic effect or death. The last examination date was defined as last date of either visit date, LAB, BM, EMD or dosage information. For a patient discontinuing study medication, the date of last dose of study medication was taken as the last examination date unless death was the reason for discontinuation in which case the date of death was taken as the last examination date.

The time to event variables were calculated using the calculated confirmed complete hematologic response and were defined as follows:

### **Time to complete hematologic response-**

This was defined for all patients with calculated confirmed complete hematologic response as the time until first documented response (which was confirmed  $\geq 4$  weeks later). This variable was not specified in the protocol but was calculated as additional analysis.

### **Duration of complete hematologic response-**

This duration was evaluated for all patients with calculated confirmed complete hematologic response and was defined as the time between first documented response (which was confirmed  $\geq 4$  weeks later) and the earliest date of the following

- loss of response (WBC  $> 20 \times 10^9/L$  or when any of the other criteria for complete hematologic response were no longer fulfilled).
- progression to blast crisis or accelerated phase
- discontinuation due to unsatisfactory therapeutic effect or death.

### **Statistical Methods**

This investigation followed a single stage procedure design according to Fleming (alpha=2.5% (one-sided) and power=90%). For hematological failures the hypotheses were: Ho:  $p \leq 10\%$  and  $H_1: p \geq 20\%$ . For cytogenetic failures the hypotheses were: Ho:  $p \leq 15\%$  and

## CLINICAL REVIEW

H<sub>1</sub>: p $\geq$ 30%. All 95% confidence intervals (CI) were calculated using Pearson-Clopper limits. Time to event variables were evaluated using the Kaplan-Meier method.

### Trial Results

#### Study Conduct

This study was performed in accordance with standard operating procedures of the sponsor (formerly Ciba/Novartis), operating at the time of the study. These were designed to ensure adherence to GCP and ensure the protection of the patients, as required by the following directives in operation at the time:

1. Declaration of Helsinki and amendments, concerning medical research in humans (Recommendations Guiding Physicians in Biomedical Research Involving Human Patients).
2. Directive 91/507/EEC: The Rules Governing Medicinal Products in the European Community.
3. US 21 Code of Federal Regulations dealing with clinical studies, parts 50 and 56, concerning Informed Patient Consent and IRB approval.

#### Informed Consent and Treatment Assignment

Informed consent was obtained from each study patient.

#### Randomization

Not applicable.

#### Blinding

Not applicable

#### Central Reviewed Pathology

Not applicable

#### Protocol Violations

Table 3 summarizes the protocol violations that were detected in the ITT population.

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## CLINICAL REVIEW

**Table 3 Protocol violations**

Protocol violations	All patients N=532	Hematologic failure N=152 (%)	Cytogenetic failure N=188 (%)	IFN intolerant N=192 (%)
No. of patients with protocol violations	154(28.9)	51(33.6)	47(25.0)	56(29.2)
Exclude from all PP efficacy analyses	88(16.5)	24(15.8)	30(16.0)	34(17.7)
Ph - at baseline	2(0.4)	1(0.7)	0	1 (0.5)
Not in the disease group as defined in the protocol	78(14.7)	19(12.5)	28(14.9)	31 (16.1)
Forbidden anti-neoplastic medication during study #	10(1.9)	5(3.3)	2(1.1)	3(1.6)
Exclude from PP analysis (hematologic)	6(1.1)	2(1.3)	1 (0.5)	3(1.6)
Less than two post-baseline efficacy assessments for hematological response (and no PD/death)	6(1.1)	2(1.3)	1 (0.5)	3(1.6)
Exclude from PP analysis (cytogenetic)	17(3.2)	9(5.9)	3(1.6)	5(2.6)
Ph - at baseline	5(0.9)	3(2.0)	1 (0.5)	1 (0.5)
No post-baseline efficacy assessments for cytogenetic response (and no PD/death)	12(2.3)	6(3.9)	2(1.1)	4(2.1)
<b>Minor protocol violations</b>	<b>74(13.9%)</b>	<b>30(19.7)</b>	<b>22(11.7)</b>	<b>22(11.5)</b>
IFN within 48 hours of day 1	24(4.5%)	13(8.6)	7(3.7)	4(2.1)
Cytosine arabinoside within seven days of day 1	5(0.9%)	1 (0.7)	3(1.6)	1 (0.5)
Busulfan within six weeks of day 1	2(0.4%)	1 (0.7)	0	1 (0.5)
Hydroxyurea within 7 days of day 1	20(3.8%)	7(4.6)	3(1.6)	10(5.2)
No documentation of Ph+ (Ph missing at baseline)	19(3.6%)	9(5.9)	6(3.2)	4(2.1)
SGOT (AST) > 3xULN	2(0.4%)	1 (0.7)	0	1 (0.5)
SGPT (ALT) > 3xULN	5(0.9%)	4(2.6)	1 (0.5)	0
Forbidden anti-neoplastics during study #	7(1.3%)	2(1.3)	3(1.6)	2(1.0)

# Consumption of anti-neoplastic medication which was considered likely to influence the efficacy evaluation was considered a major protocol violation, but consumption which was not considered likely to confound the efficacy evaluation (e.g. medication prescribed for disease progression) was classified as a minor violation.

### Enrollment, Demographics, Baseline Characteristics

#### Baseline Demographics

Table 4 provides details of demographic characteristics.

## CLINICAL REVIEW

**Table 4 Demographic summary**

Demographic variable	All patients N=532	Hematologic failure N=152	Cytogenetic failure N=188	IFN intolerant N=192
<b>Age (years)</b>				
median	57.0	55.5	53.0	59.0
25-75 <sup>th</sup> percentiles	45-64	42-63	45-62	50-67
minimum - maximum	18-90	18-79	23-77	20-90
<b>Age category (n(%))</b>				
<50 years	168(31.6)	57(37.5)	64(34.0)	47(24.5)
≥50 - <60 years	153(28.8)	38(25.0)	65(34.6)	50(26.0)
≥60 - <70 years	159(29.9)	47(30.9)	44(23.4)	68(35.4)
≥70 years	52(9.8)	10(6.6)	15(8.0)	27(14.1)
<b>Sex (n(%))</b>				
Male	311 (58.5)	102(67.1)	111 (59.0)	98(51.0)
Female	221 (41.5)	50(32.9)	77(41.0)	94(49.0)
<b>Race (n(%))</b>				
Caucasian	463(87.0)	128(84.2)	161 (85.6)	174(90.6)
Black	32(6.0)	13(8.6)	10(5.3)	9(4.7)
Oriental	8(1.5)	3(2.0)	3(1.6)	2(1.0)
Other	29(5.5)	8(5.3)	14(7.4)	7(3.6)
<b>Weight (kg)</b>				
n	526	151	186	189
median	78.15	78.40	79.7	76.8
minimum - maximum	45.0-148.6	45.0-147.2	49.0-148.6	46.8-127.8
<b>Body surface area (M<sup>2</sup>)</b>				
n	522	148	186	188
Median	1.91	1.93	1.92	1.90
minimum - maximum	1.12-2.80	1.40-2.76	1.12-2.80	1.46-2.80
<b>ECOG performance status</b>				
Missing	26(4.9)	1 (0.7)	13(6.9)	12(6.3)
Grade 0	316(59.4)	102(67.1)	118(62.8)	96(50.0)
Grade 1	172(32.3)	43(28.3)	54(28.7)	75(39.1)
Grade 2	18(3.4)	6(3.9)	3(1.6)	9(4.7)

### Disease Characteristics of the Patient Population

Table 5 summarizes pertinent data concerning disease history at baseline in the ITT population.

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**Table 5 Disease history**

Disease history	All patients N=532	Hematologic failure N=152	Cytogenetic failure N=188	IFN intolerant N=192
<b>Time since first diagnosis of CML (months)</b>				
median	32.0	32.3	32.7	29.6
minimum - maximum	3-218	3-131	10-184	3-218
<b>Time since first diagnosis of CML (n(%))</b>				
<6 months	5(0.9)	1 (0.7)	0	4(2.1)
≥6 months - <12 months	44(8.3)	20(13.2)	2(1.1)	22(11.5)
≥12 months - <24 months	145(27.3)	37(24.3)	51 (27.1)	57(29.7)
≥2 years- <5 years	226(42.5)	68(44.7)	89(47.3)	69(35.9)
≥5 years	112(21.1)	26(17.1)	46(24.5)	40(20.8)
<b>Duration of IFN at ≥25 MIU/week (months)</b>				
median	14.0	12.1	22.1	7.0
minimum - maximum	0-135	1-83	4-135	0-117
<b>Duration of IFN at ≥25 MIU/week (n(%))</b>				
<6 months	102(19.2)	21 (13.8)	1 (0.5)	80(41.7)
≥ 6 months - < 12 months	120(22.6)	54(35.5)	16(8.5)	50(26.0)
≥12 months	305(57.3)	77(50.7)	171 (91.0)	57(29.7)
<b>Time since IFN started (months)</b>				
median	0.9	0.8	1.0	0.7
minimum - maximum	0-5	0-4	0-5	0-5
<b>Time since IFN started (n(%))</b>				
<6 months	527(99.1)	152(100)	188(100)	187(97.4)
<b>Time since IFN stopped (months)</b>				
median	0.1	0.1	0.0	0.3
minimum - maximum	0-4	0-4	0-3	0-3
<b>Time since IFN stopped (n(%))</b>				
<6 months	527(99.1)	152(100)	188(100)	187(97.4)

### Enrollment by Study Center

Data not available

### Patient Exposure to Study Drug

The maximum drug exposure at the time of the data cut-off was 31.5 months, 80.5% of patients were on treatment for 24 months or more (Table 6).

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**Table 6 Duration of exposure to the study drug**

	All patients N=532
Duration of exposure (days)	
median	883.5
25th -75th percentiles	794-918
minimum - maximum	16-959
Duration of exposure (n(%))	
<6 months	20(3.8)
≥6 months - <12 months	28(5.3)
≥ 12 months - <18 months	23(4.3)
≥18 months - <24 months	33(6.2)
≥24 months	428 (80.5)

### Efficacy Results - FDA and Sponsor Assessment

#### Primary efficacy results

Table 7 shows the numbers of cytogenetic responders.

**Table 7 Cytogenetic response rates**

Response	All patients N=532(%)	Hematologic Failure N=152(%)	Cytogenetic failure N=188(%)	IFN Intolerant N=192(%)
<b>Unconfirmed response</b>				
MCyR = CCyR + PCyR	343(64.5)	82(53.9)	127(67.6)	134(69.8)
95% CI	[60.2, 68.5]	[45.7, 62.1]	[60.4, 74.2]	[62.8, 76.2]
CCyR	257(48.3)	58(38.2)	97(51.6)	102(53.1)
95% CI	[44.0, 52.6]	[30.4, 46.4]	[44.2, 58.9]	[45.8, 60.3]
PCyR	86(16.2)	24(15.8)	30(16.0)	32(16.7)
Minor	20(3.8)	5(3.3)	10(5.3)	5(2.6)
Minimal	58(10.9)	22(14.5)	19(10.1)	17(8.9)
<b>Confirmed response</b>				
MCyR = CCyR + PCyR	315(59.2)	69(45.4)	120(63.8)	126(65.6)
95% CI	[54.9, 63.4]	[37.3, 53.7]	[56.5, 70.7]	[58.4, 72.3]
CCyR	203(38.2)	45(29.6)	70(37.2)	88(45.8)
95% CI	[34.0, 42.4]	[22.5, 37.5]	[30.3, 44.6]	[38.6, 53.2]
PCyR	112(21.1)	24(15.8)	50(26.6)	38(19.8)

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### Secondary efficacy results

#### Time to and duration of MCyR and CCyR

More than half of the MCyRs were seen at the first bone marrow assessment 3 months after start of treatment. Using Kaplan-Meier estimates, the median time to MCyR was 3.2 months with 95% CI [3.0, 5.5]. The median time to CCyR was 8.3 months [5.8, 8.3]. However, 8.5% (10.5%) of patients achieved a MCyR (CCyR) only after 12 months of treatment, with 6 MCyRs and 17 CCyRs even after 2 years of treatment.

About 10% of the 343 patients who had achieved MCyR during treatment had confirmed loss of response or discontinued for progression. Of these 35 cases, 15 had achieved a CCyR (of which 7 were confirmed). Only 10 (2.9%) of the patients with MCyR progressed to AP or BC later during treatment. The estimated rate still in MCyR after 18 months is 90.0% [86.6, 93.4] and at 24 months 87.8% [83.8, 91.7].

#### Complete Hematologic Response

About 95% of the patients achieved a confirmed complete hematologic response (CHR, 95% CI [92.3, 96.3]). Responses were usually achieved within 1 month after start of treatment. Of the 503 patients with confirmed CHR, 117 (23.2%) lost response during treatment. But only 66 (13.1%) of these patients progressed to accelerated phase or blast crisis and only 64 discontinued treatment.

#### Time to accelerated phase or blast crisis

Of the 532 patients, 85 (16.0%) patients had values indicating progression to accelerated phase (AP) or blast crisis (BC), but only 67 patients (12.6%) discontinued treatment due to unsatisfactory effect. The estimated probabilities [95% CI] of being free of progression to accelerated or blast crisis are 88.4% [85.7, 91.2] at 18 months and 85.4% [82.4, and 88.5] at 24 months.

#### Overall survival

At time of analysis, 65 (12.2%) of the 532 patients had died. The survival analysis included 64 deaths (1 death was reported after BMT): 8 while on study treatment and the remaining 56 patients during follow-up after discontinuation of treatment (mostly due to progression, n=45).

The estimated probabilities [95% CI] of being alive are:

- 94.2% [92.2, 96.2] at 18 months
- 90.8% [88.3, 93.2] at 24 months.

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### D. Efficacy Conclusions

The results from this updated analysis made after a median drug exposure of approximately 29 months confirm those obtained in the submission analysis made after a median exposure of 8.3 months. Gleevec is an effective treatment for patients with chronic phase CML who had previously received interferon-alpha. Favorable treatment responses were sustained and the estimated rate of MCyR persisting for 24 months was approximately 88% and the estimated probability of being alive at 24 months was 91%. While these results are still somewhat early there is no reason, at present, to challenge the early optimism regarding Gleevec CML treatment. Continued follow-up to determine five-year survival is necessary.

## VII. Integrated Review of Safety

### A. Sponsor's Conclusions

Gleevec was generally well tolerated and no new safety concerns were identified in patients treated for more than 2 years. The most frequently reported events were those that affect the gastrointestinal, musculoskeletal systems or skin. As with the previous analysis, the most frequently reported AEs were fluid retention, nausea and muscle cramps.

The updated study showed that non-hematological AE were noted by most patients, of which greater than half experiencing one or more grade 3 or 4 events. The most common were gastrointestinal (nausea, vomiting, diarrhea, dyspepsia), musculoskeletal complaints and skin (rash, fluid retention). Most AEs were managed with anti-diarrheals, anti-inflammatory, antihistamines, diuretics, and allopurinol.

Weight gain was reported in 32.3% of patients and suspected by investigators of being related to study treatment in 28.9% of the patients. The weight gains were noted to occur steadily over time.

The most frequently reported hematological disorders were grade 3 lymphocytopenia and grade 3 and 4 neutropenia or thrombocytopenia. The duration was usually between 2-4 weeks.

AEs other than those associated with disease progression that led to premature discontinuation of therapy were relatively rare. The frequent reason for premature discontinuation of therapy was blood and lymphatic system disorders and neoplasms (disease progression).

Furthermore, the majority of deaths recorded during the study period or within 28 days of the last administration of drug was due to direct or indirect result of progression of the underlying disease.

Overall, there are no additional safety concerns noted with the additional follow-up.

## CLINICAL REVIEW

### C. Methods and Specific Findings of Safety Review

Safety assessments consisted of monitoring and recording all adverse events (AEs) and SAEs (with their severity and relationship to study drug), the regular monitoring of hematology, and blood chemistry, regular measurement of vital signs, the performance of physical examinations and documentation of all concomitant medications and therapies.

### D. Adequacy of Safety Testing

Complete safety data is available.

### E. Summary of Critical Safety Findings and Limitations of Data

Table 8 lists the non-hematological AEs by preferred term and/or grouped term in descending order of frequency which were reported to occur in >10% of patients in the Safety population. Events were listed as all events and those with CTC grade 3 or 4. In addition, those AEs with start date after 2 years are summarized.

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**Table 8** Number of patients (>10%) with most frequent non-hematologic AEs

Preferred term / Group	All patients N=532 (%)		≥2 years treated N=428 (%)
	All grades	CTC grade 3 or 4	after 2 yrs on treatment
Fluid retention*	365(68.6)	19(3.6)	39(9.1)
- Superficial edemas*	359(67.5)	11 (2.1)	36(8.4)
- Other fluid retention events*	38(7.1)	9(1.7)	4(0.9)
Nausea	335(63.0)	14(2.6)	30(7.0)
Muscle cramps*	328(61.7)	9(1.7)	27(6.3)
Diarrhea	257(48.3)	15(2.8)	28(6.5)
Fatigue	255(47.9)	6(1.1)	22(5.1)
Rash and related terms*	252(47.4)	17(3.2)	26(6.1)
Joint pain (Arthralgia)*	214(40.2)	7(1.3)	9(2.1)
Musculoskeletal pain*	204(38.3)	13(2.4)	24(5.6)
Headache	194(36.5)	3(0.6)	14(3.3)
Vomiting	189(35.5)	11 (2.1)	21 (4.9)
Weight increased	172(32.3)	36(6.8)	14(3.3)
Abdominal pain*	169(31.8)	6(1.1)	13(3.0)
Hemorrhages*	160(30.1)	12(2.3)	22(5.1)
- GI hemorrhages*	11 (2.1)	2(0.4)	1 (0.2)
- CNS hemorrhages*	9(1.7)	7(1.3)	2(0.5)
Dyspepsia	145(27.3)	0	8(1.9)
Myalgia*	144(27.1)	1 (0.2)	4(0.9)
Nasopharyngitis	115(21.6)	1 (0.2)	18(4.2)
Pyrexia	110(20.7)	10(1.9)	11 (2.6)
Cough	106(19.9)	0	8(1.9)
Upper respiratory tract infection	98 (18.4)	0	8(1.9)
Dizziness	85(16.0)	1 (0.2)	12(2.8)
Pharyngitis	82(15.4)	0	7(1.6)
Asthenia	78(14.7)	1 (0.2)	8(1.9)
Insomnia	77(14.5)	1 (0.2)	4(0.9)
Pruritus	74(13.9)	4(0.8)	5(1.2)
Night sweats	72(13.5)	1 (0.2)	11 (2.6)
Dyspnea NOS	62(11.7)	5(0.9)	6(1.4)
Chest pain	57(10.7)	4(0.8)	3(0.7)
Influenza	56(10.5)	1 (0.2)	3(0.7)

\* = grouped terms

Table 9 summarizes the numbers of patients who died or suffered non-fatal SAEs or other AEs, which were considered clinically significant since they resulted in dose reduction or interruption or led to premature discontinuation of therapy with the study drug.

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**Table 9 Numbers (%) of patients who died, had other serious or clinically significant AEs or discontinued because of AEs**

Serious or significant events	All patients N=532 (%)
Deaths during study	65(12.2)
Deaths reported as primary reason for discontinuation of study drug	8(1.5)
Deaths within 28 days of last dose of study drug	11 (2.1)
Deaths more than 28 days of last dose of study drug	46(8.6)
SAE's (fatal or non-fatal)	161 (30.3)
Study-drug-related SAEs	41 (7.7)
AEs causing discontinuation	37(7.0)
Primary reason (AE or LAB)	24(4.5)*
Contributing reason (progressive disease)	13(2.4)
Study-drug-related AEs causing discontinuation	21 (3.9)
AEs causing dose adjustment/interruption	282(53.0)

\* 7 additional patients discontinued due to lab abnormality, but did not have AEs with action taken = drug discontinued

Table 10 summarizes the principal causes of death for all patients who died during the stud) period or within 28 days after the last administration of the study drug.

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**Table 10 Deaths during treatment or within 28 days after the last study drug**

Cause of death (system organ class / preferred term)	All patients N=532 (%)
Any system organ class	19(3.6)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	8(1.5)
-Lung cancer stage unspecified	1 (0.2)
-Malignant neoplasm aggravated	2(0.4)
-Study indication	5(0.9)
Nervous system disorders	5(0.9)
-Cerebral hemorrhage	3(0.6)
-Cerebrovascular accident	1 (0.2)
-Subarachnoid hemorrhage NOS	1 (0.2)
Cardiac disorders	3(0.6)
-Arrhythmia NOS	1 (0.2)
-Cardio-respiratory arrest	1 (0.2)
-Cardiogenic shock	1 (0.2)
<b>General disorders</b>	1 (0.2)
-Death unexplained	1 (0.2)
<b>Infections and infestations</b>	1 (0.2)
-Septic shock	1 (0.2)
<b>Respiratory disorders</b>	1 (0.2)
-Pulmonary embolism	1 (0.2)

Table 11 shows the numbers of patients in the safety population who were reported to experience new or worsening CTC grade 3 or 4 hematological abnormalities during the course of the investigation and after 2 years of treatment (considering their last value before 2 years as new baseline value).

**Table 11 Number (%) of patients with grade 3 or 4 hematological abnormalities**

Hematological abnormality	All patients N = 532 (%)		All patients on treatment ≥2 year N = 428 (%)	
	Grade 3	Grade 4	Grade 3	Grade 4
Anemia	34(6.4)	7(1.3)	3(0.7)	0
Thrombocytopenia	110(20.7)	5(0.9)	9(2.1)	0
Leucopenia	119(22.4)	9(1.7)	(0.9)	0
Neutropenia	145(27.3)	46(8.6)	18(4.2)	2(0.5)
Lymphocytopenia	166(31.2)	0	22(5.1)	0

The median time to first CTC grade 3 or 4 neutropenia, thrombocytopenia and leukopenia were between 8 and 9 weeks. Anemia was first seen at a median of 20 weeks. Duration of grade 3 or 4 hematologic abnormalities was usually between 2-4 weeks.

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Table 12 shows the numbers of patients in the safety population who were reported to experience new or worsening CTC grade 3 or 4 biochemical abnormalities during the course of the investigation and after 2 years of treatment (considering their last value before 2 years as new baseline value).

**Table 12 Number (%) of patients with grade 3 or 4 biochemical abnormalities**

Biochemical abnormality	All patients		All patients on treatment 2 years	
	N = 532		N = 428 (%)	
	Grade 3	Grade 4	Grade 3	Grade 4
Hypoalbuminemia	5(0.9)	0	1(0.2)	0
Hypercreatinemia	1(0.2)	0	0	0
Hyperbilirubinemia	3(0.6)	0	1(0.2)	0
Elevated alkaline phosphatase	1(0.2)	0	0	0
SGOT (AST) increase	12(2.3)	0	0	0
SGPT (ALT) increase	11(2.1)	0	1 (0.2)	0

### VIII. Dosing, Regimen, and Administration Issues

Not applicable

### IX. Use in Special Populations

#### A. Evaluation of Sponsor's Gender Effects Analyses and Adequacy of Investigation

Analyses were appropriate and adequate.

#### B. Evaluation of Evidence for Age, Race, or Ethnicity Effects on Safety or Efficacy

##### 1. Age

Analyses were appropriate and adequate.

##### 2. Race/Ethnicity

Approximately 85% to 90% of study participants were Caucasian, 6% were Black, 2% were Oriental. Aside from Caucasians there is insufficient information for other patient populations.

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### C. Evaluation of Pediatric Program

Pediatric studies are ongoing and are adequate.

### D. Comments on Data Available or Needed in Other Populations

#### 1. Renal or Hepatic Impairment

A hepatic impairment PK study is ongoing..

#### 2. Pregnancy

Adequate data is available.

## X. Conclusions and Recommendations

### A. Conclusions

The current analysis, made after a median drug exposure of approximately 29 months, confirm results of the submission analysis made after a median exposure of 8.3 months. In patients with Ph+ CML treatment with Gleevec at an initial dose of 400 mg once daily was associated with a complete hematologic response (CHR) in 95% of patients. The confirmed (second evaluation after  $\geq 4$  weeks) major cytogenetic response rates (MCyR) was 60%. The confirmed complete cytogenetic response (CCyR) rate was 39%. The favorable responses were sustained and the estimated rate of MCyR persisting for 24 months was approximately 88%, CHR persisting for 24 months was between 66% and 84% and the estimated probability of being alive at 24 months was 91%. Gleevec was generally well tolerated and no new safety concerns were identified in patients treated for more than 2 years.

### B. Recommendations

#### 1. Approval

The Division of Oncology Drug Products (DODP), Center for Drug Evaluation and Research (CDER), FDA recommends the conversion of the 2<sup>nd</sup> line chronic phase CML indication to full approval status. This recommendation is made because there appears to be clinical benefit, as indicated by sustained cytogenetic remissions in patients who are protocol defined interferon alpha failures (patients had received a median of 14 months of prior IFN therapy at therapeutic dose [ $\geq 25 \times 10^6$  IU/week] and were all in late chronic phase, with a median time from diagnosis of 32 months). Continued follow-up to determine five-year survival is still indicated.

#### 2. Binding phase 4 commitments

None.

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**XI. Appendix**

The proposed revised Gleevec package insert with updated data for the conversion of 2<sup>nd</sup> line CML indication to full approval status has been submitted.

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MEDICAL OFFICER

John Johnson  
11/5/03 12:58:53 PM  
MEDICAL OFFICER