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4 **Gleevec®**  
5 **(imatinib mesylate)**

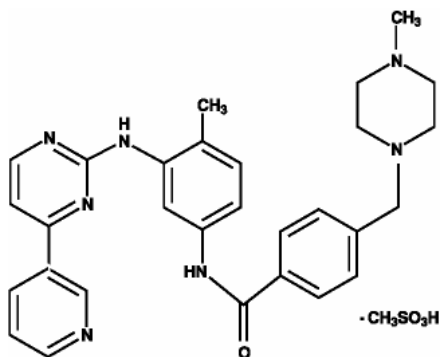
6 **Tablets**

7 **Rx only**

8 **Prescribing Information**

9 **DESCRIPTION**

10 Gleevec® (imatinib mesylate) film-coated tablets contain imatinib mesylate equivalent to  
11 100 mg or 400 mg of imatinib free base. Imatinib mesylate is designated chemically as 4-[(4-  
12 Methyl-1-piperazinyl)methyl]-N-[4-methyl-3-[[4-(3-pyridinyl)-2-pyrimidinyl]amino]-  
13 phenyl]benzamide methanesulfonate and its structural formula is



14  
15 Imatinib mesylate is a white to off-white to brownish or yellowish tinged crystalline  
16 powder. Its molecular formula is  $C_{29}H_{31}N_7O \cdot CH_4SO_3$  and its molecular weight is 589.7.  
17 Imatinib mesylate is soluble in aqueous buffers  $\leq$  pH 5.5 but is very slightly soluble to  
18 insoluble in neutral/alkaline aqueous buffers. In non-aqueous solvents, the drug substance is  
19 freely soluble to very slightly soluble in dimethyl sulfoxide, methanol and ethanol, but is  
20 insoluble in n-octanol, acetone and acetonitrile.

21 **Inactive Ingredients:** colloidal silicon dioxide (NF); crospovidone (NF);  
22 hydroxypropyl methylcellulose (USP); magnesium stearate (NF); and microcrystalline  
23 cellulose (NF). *Tablet coating:* ferric oxide, red (NF); ferric oxide, yellow (NF);  
24 hydroxypropyl methylcellulose (USP); polyethylene glycol (NF) and talc (USP).

## 25 CLINICAL PHARMACOLOGY

### 26 Mechanism of Action

27 Imatinib mesylate is a protein-tyrosine kinase inhibitor that inhibits the Bcr-Abl tyrosine  
28 kinase, the constitutive abnormal tyrosine kinase created by the Philadelphia chromosome  
29 abnormality in chronic myeloid leukemia (CML). It inhibits proliferation and induces  
30 apoptosis in Bcr-Abl positive cell lines as well as fresh leukemic cells from Philadelphia  
31 chromosome positive chronic myeloid leukemia. In colony formation assays using *ex vivo*  
32 peripheral blood and bone marrow samples, imatinib shows inhibition of Bcr-Abl positive  
33 colonies from CML patients.

34 *In vivo*, it inhibits tumor growth of Bcr-Abl transfected murine myeloid cells as well  
35 as Bcr-Abl positive leukemia lines derived from CML patients in blast crisis.

36 Imatinib is also an inhibitor of the receptor tyrosine kinases for platelet-derived  
37 growth factor (PDGF) and stem cell factor (SCF), c-kit, and inhibits PDGF- and  
38 SCF-mediated cellular events. *In vitro*, imatinib inhibits proliferation and induces apoptosis in  
39 gastrointestinal stromal tumor (GIST) cells, which express an activating c-kit mutation.

### 40 Pharmacokinetics

41 The pharmacokinetics of Gleevec<sup>®</sup> (imatinib mesylate) have been evaluated in studies in  
42 healthy subjects and in population pharmacokinetic studies in over 900 patients. Imatinib  
43 is well absorbed after oral administration with  $C_{max}$  achieved within 2-4 hours post-dose. Mean  
44 absolute bioavailability is 98%. Following oral administration in healthy volunteers, the  
45 elimination half-lives of imatinib and its major active metabolite, the N-desmethyl derivative,  
46 are approximately 18 and 40 hours, respectively. Mean imatinib AUC increases  
47 proportionally with increasing doses ranging from 25 mg-1000 mg. There is no significant  
48 change in the pharmacokinetics of imatinib on repeated dosing, and accumulation is 1.5-2.5  
49 fold at steady state when Gleevec is dosed once daily. At clinically relevant concentrations of  
50 imatinib, binding to plasma proteins in *in vitro* experiments is approximately 95%, mostly to  
51 albumin and  $\alpha_1$ -acid glycoprotein.

52 The pharmacokinetics of Gleevec are similar in CML and GIST patients.

### 53 Metabolism and Elimination

54 CYP3A4 is the major enzyme responsible for metabolism of imatinib. Other cytochrome P450  
55 enzymes, such as CYP1A2, CYP2D6, CYP2C9, and CYP2C19, play a minor role in its  
56 metabolism. The main circulating active metabolite in humans is the N-demethylated  
57 piperazine derivative, formed predominantly by CYP3A4. It shows *in vitro* potency similar to  
58 the parent imatinib. The plasma AUC for this metabolite is about 15% of the AUC for  
59 imatinib.

60 Elimination is predominately in the feces, mostly as metabolites. Based on the  
61 recovery of compound(s) after an oral <sup>14</sup>C-labeled dose of imatinib, approximately 81% of the  
62 dose was eliminated within 7 days, in feces (68% of dose) and urine (13% of dose).  
63 Unchanged imatinib accounted for 25% of the dose (5% urine, 20% feces), the remainder  
64 being metabolites.

65 Typically, clearance of imatinib in a 50-year-old patient weighing 50 kg is expected to  
66 be 8 L/h, while for a 50-year-old patient weighing 100 kg the clearance will increase to  
67 14 L/h. However, the inter-patient variability of 40% in clearance does not warrant initial  
68 dose adjustment based on body weight and/or age but indicates the need for close monitoring  
69 for treatment related toxicity.

## 70 **Special Populations**

71 **Pediatric:** As in adult patients, imatinib was rapidly absorbed after oral administration in  
72 pediatric patients, with a  $C_{max}$  of 2-4 hours. Apparent oral clearance was similar to adult  
73 values (11.0 L/hr/m<sup>2</sup> in children vs. 10.0 L/hr/m<sup>2</sup> in adults), as was the half-life (14.8 hours in  
74 children vs. 17.1 hr in adults). Dosing in children at both 260 mg/m<sup>2</sup> and 340 mg/m<sup>2</sup> achieved  
75 an AUC similar to the 400-mg dose in adults. The comparison of AUC<sub>(0-24)</sub> on Day 8 vs. Day  
76 1 at 260 mg/m<sup>2</sup> and 340 mg/m<sup>2</sup> dose levels revealed a 1.5 and 2.2-fold drug accumulation,  
77 respectively, after repeated once-daily dosing. Mean imatinib AUC did not increase  
78 proportionally with increasing dose.

79 **Hepatic Insufficiency:** No clinical studies were conducted with Gleevec in patients with  
80 impaired hepatic function.

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

## 85 **Drug-Drug Interactions**

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

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

93 **CYP3A4 Inducers:** Pretreatment of 14 healthy volunteers with multiple doses of rifampin,  
94 600 mg daily for 8 days, followed by a single 400 mg dose of Gleevec, increased Gleevec  
95 oral-dose clearance by 3.8-fold (90% confidence interval = 3.5- to 4.3-fold), which represents  
96 mean decreases in  $C_{max}$ , AUC<sub>(0-24)</sub> and AUC<sub>(0-∞)</sub> by 54%, 68% and 74%, of the respective  
97 values without rifampin treatment. (See PRECAUTIONS and DOSAGE AND  
98 ADMINISTRATION.)

99 **In Vitro Studies of CYP Enzyme Inhibition:** Human liver microsome studies demonstrated  
100 that Gleevec is a potent competitive inhibitor of CYP2C9, CYP2D6, and CYP3A4/5 with  $K_i$   
101 values of 27, 7.5 and 8 μM, respectively. Gleevec is likely to increase the blood level of drugs  
102 that are substrates of CYP2C9, CYP2D6 and CYP3A4/5. (See PRECAUTIONS.)

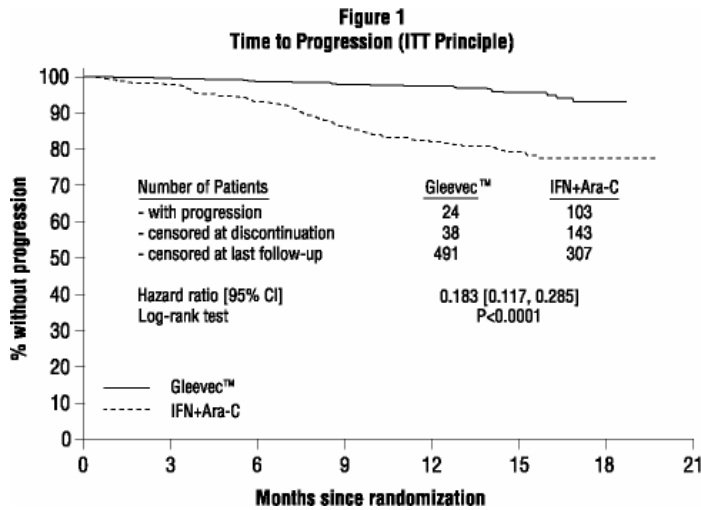
103 **CLINICAL STUDIES**104 **Chronic Myeloid Leukemia**105 ***Chronic Phase, Newly Diagnosed***

106 An open-label, multicenter, international randomized Phase 3 study has been conducted in  
 107 patients with newly diagnosed Philadelphia chromosome positive (Ph+) chronic myeloid  
 108 leukemia (CML) in chronic phase. This study compared treatment with either single-agent  
 109 Gleevec® (imatinib mesylate) or a combination of interferon-alfa (IFN) plus cytarabine  
 110 (Ara-C). Patients were allowed to cross over to the alternative treatment arm if they failed to  
 111 show a complete hematologic response (CHR) at 6 months, a major cytogenetic response  
 112 (MCyR) at 12 months, or if they lost a CHR or MCyR. Patients with increasing WBC or  
 113 severe intolerance to treatment were also allowed to cross over to the alternative treatment  
 114 arm with the permission of the study monitoring committee (SMC). In the Gleevec arm,  
 115 patients were treated initially with 400 mg daily. In the IFN arm, patients were treated with a  
 116 target dose of IFN of 5 MIU/m<sup>2</sup>/day subcutaneously in combination with subcutaneous Ara-C  
 117 20 mg/m<sup>2</sup>/day for 10 days/month.

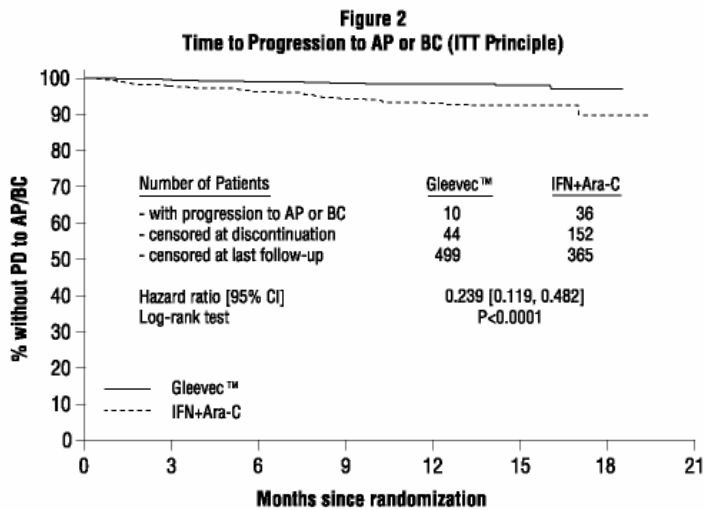
118 A total of 1106 patients were randomized from 177 centers in 16 countries, 553 to  
 119 each arm. Baseline characteristics were well balanced between the two arms. Median age was  
 120 51 years (range 18-70 years), with 21.9% of patients ≥60 years of age. There were 59% males  
 121 and 41% females; 89.9% Caucasian and 4.7% Black patients. With a median follow-up of 14  
 122 and 13 months for Gleevec and IFN, respectively, 90% of patients randomized to Gleevec  
 123 were still receiving first-line treatment. Due to discontinuations and cross-overs, only 30% of  
 124 patients randomized to IFN were still on first-line treatment. In the IFN arm, withdrawal of  
 125 consent (13.4%) was the most frequent reason for discontinuation of first-line therapy, and the  
 126 most frequent reason for cross over to the Gleevec arm was severe intolerance to treatment  
 127 (22.8%). [1]

Comment: This corrects a typo from 22.7 to 22.8%

128 The primary efficacy endpoint of the study was progression-free survival (PFS). The  
 129 final analysis of progression-free survival was planned after 5 years, however, the reported  
 130 analysis was conducted at one year after the last patient was randomized to the study.  
 131 Progression was defined as any of the following events: progression to accelerated phase or  
 132 blast crisis, death, loss of CHR or MCyR, or in patients not achieving a CHR an increasing  
 133 WBC despite appropriate therapeutic management. The protocol specified that the  
 134 progression analysis would compare the intent to treat (ITT) population: patients randomized  
 135 to receive Gleevec were compared with patients randomized to receive interferon. Patients  
 136 that crossed over prior to progression were not censored at the time of cross-over, and events  
 137 that occurred in these patients following cross-over were attributed to the original randomized  
 138 treatment. A total of 218 patients crossed over from the interferon arm to the Gleevec arm,  
 139 and 7 patients crossed over from the Gleevec arm to the interferon arm. The estimated rate of  
 140 progression-free survival at 12 months in the ITT population was 97.2% in the Gleevec arm  
 141 and 80.3% in the control arm. (Figure 1.) The estimated rate of patients free of progression to  
 142 accelerated phase (AP) or blast crisis (BC) at 12 months was 98.5% in the Gleevec arm  
 143 compared to the 93.1% in the IFN arm. (Figure 2.) There were 11 and 20 deaths reported in  
 144 the Gleevec and IFN arm, respectively.



145  
146



147

148 Major cytogenetic response, hematologic response, time to accelerated phase or blast  
149 crisis and survival were main secondary endpoints. Response data are shown in Table 1.  
150 Complete hematologic response, major cytogenetic response and complete cytogenetic  
151 response were also statistically significantly higher in the Gleevec arm compared to the IFN +  
152 Ara-C arm.

153 **Table 1 Response in Newly Diagnosed CML Study (First-Line)**

154	<b>Gleevec<sup>®</sup></b>	<b>IFN+Ara-C</b>
155	n=553	n=553
156	<b>(Best Response Rates)</b>	
156	<b>Hematologic Response<sup>1</sup></b>	
157	522 (94.4%)*	302 (54.6%)*
158	[92.1%, 96.2%]	[50.4%, 58.8%]
159	<b>Cytogenetic Response<sup>2</sup></b>	
160	<b>Major Cytogenetic Response n (%)</b>	
161	419 (75.8%)*	67 (12.1%)*
162	[72.0%, 79.3%]	[9.5%, 15.1%]
162	Unconfirmed <sup>3</sup>	
162	82.6%*	20.3%*
163	<b>Complete Cytogenetic Response n (%)</b>	
164	297 (53.7%)*	15 (2.7%)*
164	Unconfirmed <sup>3</sup>	
164	67.8%*	7.4%*

165 \* p&lt;0.001, Fischer's exact test

166 <sup>1</sup> **Hematologic response criteria (all responses to be confirmed after ≥4 weeks):**167 WBC<10 x 10<sup>9</sup>/L, platelet <450 x 10<sup>9</sup>/L, myelocyte + metamyelocyte <5% in blood, no blasts and  
168 promyelocytes in blood, basophils <20%, no extramedullary involvement.169 <sup>2</sup> **Cytogenetic response criteria (confirmed after ≥4 weeks):** complete (0% Ph+ metaphases) or  
170 partial (1%-35%). A major response (0%-35%) combines both complete and partial responses.171 <sup>3</sup> Unconfirmed cytogenetic response is based on a single bone marrow cytogenetic evaluation,  
172 therefore unconfirmed complete or partial cytogenetic responses might have had a lesser  
173 cytogenetic response on a subsequent bone marrow evaluation.

174 Physical, functional, and treatment-specific biologic response modifier scales from the  
175 FACT-BRM (Functional Assessment of Cancer Therapy - Biologic Response Modifier)  
176 instrument were used to assess patient-reported general effects of interferon toxicity in 1067  
177 patients with CML in chronic phase. After one month of therapy to six months of therapy,  
178 there was a 13%-21% decrease in median index from baseline in patients treated with  
179 interferon, consistent with increased symptoms of interferon toxicity. There was no apparent  
180 change from baseline in median index for patients treated with Gleevec.

181 **Late Chronic Phase CML and Advanced Stage CML**

182 Three international, open-label, single-arm Phase 2 studies were conducted to determine the  
183 safety and efficacy of Gleevec in patients with Ph+ CML: 1) in the chronic phase after failure  
184 of IFN therapy, 2) in accelerated phase disease, or 3) in myeloid blast crisis. About 45% of  
185 patients were women and 6% were Black. In clinical studies 38%-40% of patients were ≥60  
186 years of age and 10%-12% of patients were ≥70 years of age.

187 **Chronic Phase, Prior Interferon-Treatment**

188 532 patients were treated at a starting dose of 400 mg; dose escalation to 600 mg was allowed.  
189 The patients were distributed in three main categories according to their response to prior  
190 interferon: failure to achieve (within 6 months), or loss of a complete hematologic response  
191 (29%), failure to achieve (within 1 year) or loss of a major cytogenetic response (35%), or  
192 intolerance to interferon (36%). Patients had received a median of 14 months of prior IFN  
193 therapy at doses ≥25 x 10<sup>6</sup> IU/week and were all in late chronic phase, with a median time  
194 from diagnosis of 32 months. Effectiveness was evaluated on the basis of the rate of  
195 hematologic response and by bone marrow exams to assess the rate of major cytogenetic  
196 response (up to 35% Ph+ metaphases) or complete cytogenetic response (0% Ph+

197 metaphases). Median duration of treatment was 29 months with 81% of patients treated for  
198  $\geq 24$  months (maximum = 31.5 months).[2] Efficacy results are reported in Table 2. Confirmed  
199 major cytogenetic response rates were higher in patients with IFN intolerance (66%) and  
200 cytogenetic failure (64%), than in patients with hematologic failure (47%). Hematologic  
201 response was achieved in 98% of patients with cytogenetic failure, 94% of patients with  
202 hematologic failure, and 92% of IFN-intolerant patients [3].

### 203 **Accelerated Phase**

204 235 patients with accelerated phase disease were enrolled. These patients met one or more of  
205 the following criteria:  $\geq 15\%$ - $<30\%$  blasts in PB or BM;  $\geq 30\%$  blasts + promyelocytes in PB  
206 or BM;  $\geq 20\%$  basophils in PB; and  $<100 \times 10^9/L$  platelets. The first 77 patients were started at  
207 400 mg, with the remaining 158 patients starting at 600 mg.

208 Effectiveness was evaluated primarily on the basis of the rate of hematologic response,  
209 reported as either complete hematologic response, no evidence of leukemia (i.e., clearance of  
210 blasts from the marrow and the blood, but without a full peripheral blood recovery as for  
211 complete responses), or return to chronic phase CML. Cytogenetic responses were also  
212 evaluated. Median duration of treatment was 18 months with 45% of patients treated for  $\geq 24$   
213 months (maximum = 35 months). [4]Efficacy results are reported in Table 2. Response rates  
214 in accelerated phase CML were higher for the 600-mg dose group than for the 400 mg group:  
215 hematologic response (75% vs. 64%), confirmed and unconfirmed major cytogenetic response  
216 (31% vs. 19%).[5]

### 217 **Myeloid Blast Crisis**

218 260 patients with myeloid blast crisis were enrolled. These patients had  $\geq 30\%$  blasts in PB or  
219 BM and/or extramedullary involvement other than spleen or liver; 95 (37%) had received  
220 prior chemotherapy for treatment of either accelerated phase or blast crisis (“pretreated  
221 patients”) whereas 165 (63%) had not (“untreated patients”). The first 37 patients were started  
222 at 400 mg; the remaining 223 patients were started at 600 mg.

223 Effectiveness was evaluated primarily on the basis of rate of hematologic response,  
224 reported as either complete hematologic response, no evidence of leukemia, or return to  
225 chronic phase CML using the same criteria as for the study in accelerated phase. Cytogenetic  
226 responses were also assessed. Median duration of treatment was 4 months with 21% of  
227 patients treated for  $\geq 12$  months and 10% for  $\geq 24$  months (maximum = 35 months).[6]  
228 Efficacy results are reported in Table 2. The hematologic response rate was higher in  
229 untreated patients than in treated patients (36% vs. 22%, respectively) and in the group  
230 receiving an initial dose of 600 mg rather than 400 mg (33% vs. 16%). The confirmed and  
231 unconfirmed major cytogenetic response rate was also higher for the 600-mg dose group than  
232 for the 400 mg group (17% vs. 8%).

233 **Table 2 Response in CML Studies [7]**

	<b>Chronic Phase IFN Failure (n=532)</b>	<b>Accelerated Phase (n=235)</b>	<b>Myeloid Blast Crisis (n=260)</b>
	<b>400 mg</b>	<b>600 mg n=158 400 mg n=77</b>	<b>600 mg n=223 400 mg n=37</b>
	<b>% of patients [CI<sub>95%</sub>]</b>		
<b>Hematologic Response<sup>1</sup></b>	<b>95% [92.3-96.3]</b>	<b>71% [64.8-76.8]</b>	<b>31% [25.2-36.8]</b>
Complete Hematologic Response (CHR)	95%	38%	7%
No Evidence of Leukemia (NEL)	Not applicable	13%	5%
Return to Chronic Phase (RTC)	Not applicable	20%	18%
<b>Major Cytogenetic Response<sup>2</sup></b>	<b>60% [55.3-63.8]</b>	<b>21% [16.2-27.1]</b>	<b>7% [4.5-11.2]</b>
(Unconfirmed <sup>3</sup> )	(65%)	(27%)	(15%)
Complete <sup>4</sup> (Unconfirmed <sup>3</sup> )	39% (47%)	16% (20%)	2% (7%)

249 <sup>1</sup> **Hematologic response criteria (all responses to be confirmed after ≥4 weeks):**

250 CHR: Chronic phase study [WBC <10 x 10<sup>9</sup>/L, platelet <450 x 10<sup>9</sup>/L, myelocytes + metamyelocytes  
251 <5% in blood, no blasts and promyelocytes in blood, basophils <20%, no extramedullary  
252 involvement] and in the accelerated and blast crisis studies [ANC ≥1.5 x 10<sup>9</sup>/L, platelets ≥100 x  
253 10<sup>9</sup>/L, no blood blasts, BM blasts <5% and no extramedullary disease]

254 NEL: same criteria as for CHR but ANC ≥1 x 10<sup>9</sup>/L and platelets ≥20 x 10<sup>9</sup>/L (accelerated and blast  
255 crisis studies)

256 RTC: <15% blasts BM and PB, <30% blasts + promyelocytes in BM and PB, <20% basophils in PB,  
257 no extramedullary disease other than spleen and liver (accelerated and blast crisis studies).

258 BM=bone marrow, PB=peripheral blood

259 <sup>2</sup> **Cytogenetic response criteria (confirmed after ≥4 weeks):** complete (0% Ph+ metaphases) or  
260 partial (1%-35%). A major response (0%-35%) combines both complete and partial responses.

261 <sup>3</sup> Unconfirmed cytogenetic response is based on a single bone marrow cytogenetic evaluation,  
262 therefore unconfirmed complete or partial cytogenetic responses might have had a lesser  
263 cytogenetic response on a subsequent bone marrow evaluation.

264 <sup>4</sup> Complete cytogenetic response confirmed by a second bone marrow cytogenetic evaluation  
265 performed at least one month after the initial bone marrow study.

266 The median time to hematologic response was 1 month. In late chronic phase CML,  
267 with a median time from diagnosis of 32 months, an estimated 87.8% of patients who  
268 achieved MCyR maintain their response 2 years after achieving their initial response. After 2  
269 years of treatment, an estimated 85.4% of patients were free of progression to AP or BC, and  
270 estimated overall survival was 90.8% [88.3, 93.2]. [8] In accelerated phase, median duration of  
271 hematologic response was 28.8 months for patients with an initial dose of 600 mg (16.5  
272 months for 400 mg, p=0.0035). An estimated 63.8% of patients who achieved MCyR were  
273 still in response 2 years after achieving initial response. The median survival was 20.9 [13.1,  
274 34.4] months for the 400 mg group and was not yet reached for the 600 mg group (p=0.0097).  
275 An estimated 46.2% [34.7, 57.7] vs. 65.8% [58.4, 73.3] of patients were still alive after 2  
276 years of treatment in the 400 mg vs. 600 mg dose groups, respectively (p=0.0088). In blast  
277 crisis, the estimated median duration of hematologic response is 10 months. An estimated  
278 27.2% [16.8, 37.7] of hematologic responders maintained their response 2 years after  
279 achieving their initial response. Median survival was 6.9 [5.8, 8.6] months, and an estimated  
280 18.3% [13.4, 23.3] of all patients with blast crisis were alive 2 years after start of study.



281 Efficacy results were similar in men and women and in patients younger and older  
282 than age 65. Responses were seen in Black patients, but there were too few Black patients to  
283 allow a quantitative comparison.

#### 284 **Pediatric CML**

285 One open-label, single arm study enrolled 14 pediatric patients with Ph+ chronic phase CML  
286 recurrent after stem cell transplant or resistant to alpha interferon therapy. Patients ranged in  
287 age from 3 to 20 years old; 3 were 3-11 years old, 9 were 12-18 years old, and 2 were >18  
288 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),  
289 440 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  
290 are available, 4 achieved a major cytogenetic response, 7 achieved a complete cytogenetic  
291 response, and 2 had minimal cytogenetic response. At the recommended dose of  
292 260 mg/m<sup>2</sup>/day, 2 of 3 patients achieved a complete cytogenetic response. Cytogenetic  
293 response rate was similar at all dose levels.

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

#### 296 **Gastrointestinal Stromal Tumors**

297 One open-label, multinational study was conducted in patients with unresectable or metastatic  
298 malignant gastrointestinal stromal tumors (GIST). In this study 147 patients were enrolled and  
299 randomized to receive either 400 mg or 600 mg orally q.d. for up to 24 months. The study was  
300 not powered to show a statistically significant difference in response rates between the two  
301 dose groups. Patients ranged in age from 18 to 83 years old and had a pathologic diagnosis of  
302 Kit-positive unresectable and/or metastatic malignant GIST. Immunohistochemistry was  
303 routinely performed with Kit antibody (A-4502, rabbit polyclonal antiserum, 1:100; DAKO  
304 Corporation, Carpinteria, CA) according to analysis by an avidin-biotin-peroxidase complex  
305 method after antigen retrieval.

306 The primary outcome of the study was objective response rate. Tumors were required  
307 to be measurable at entry in at least one site of disease, and response characterization was  
308 based on Southwestern Oncology Group (SWOG) criteria. Results are shown in Table 3.

309 **Table 3 Tumor Response in GIST Study**

310	<b>Total Patients</b>	<b>N</b>	<b>Confirmed Partial Response N (%)</b>	<b>95% Confidence Interval</b>
311	400 mg daily	73	24 (33%)	22%, 45%
312	600 mg daily	74	32 (43%)	32%, 55%
313	<b>Total</b>	<b>147</b>	<b>56 (38%)</b>	<b>30%, 46%</b>

314 A statistically significant difference in response rates between the two dose groups  
315 was not demonstrated. At the time of interim analysis, when the median follow-up was less  
316 than 7 months, 55 of 56 patients with a confirmed partial response (PR) had a maintained PR.  
317 The data were too immature to determine a meaningful response duration. No responses were  
318 observed in 12 patients with progressive disease on 400 mg daily whose doses were increased  
319 to 600 mg daily.

## 320 **INDICATIONS AND USAGE**

321 Gleevec<sup>®</sup> (imatinib mesylate) is indicated for the treatment of newly diagnosed adult patients  
322 with Philadelphia chromosome positive chronic myeloid leukemia (CML) in chronic phase.  
323 Follow-up is limited.

324 Gleevec is also indicated for the treatment of patients with Philadelphia chromosome  
325 positive chronic myeloid leukemia (CML) in blast crisis, accelerated phase, or in chronic  
326 phase after failure of interferon-alpha therapy. Gleevec is also indicated for the treatment of  
327 pediatric patients with Ph+ chronic phase CML whose disease has recurred after stem cell  
328 transplant or who are resistant to interferon alpha therapy. There are no controlled trials in  
329 pediatric patients [9]demonstrating a clinical benefit, such as improvement in disease-related  
330 symptoms or increased survival.

331 Gleevec is also indicated for the treatment of patients with Kit (CD117) positive  
332 unresectable and/or metastatic malignant gastrointestinal stromal tumors (GIST). (See  
333 CLINICAL STUDIES: Gastrointestinal Stromal Tumors.) The effectiveness of Gleevec in  
334 GIST is based on objective response rate (see CLINICAL STUDIES). There are no controlled  
335 trials demonstrating a clinical benefit, such as improvement in disease-related symptoms or  
336 increased survival.

## 337 **CONTRAINDICATIONS**

338 Use of Gleevec<sup>®</sup> (imatinib mesylate) is contraindicated in patients with hypersensitivity to  
339 imatinib or to any other component of Gleevec.

## 340 **WARNINGS**

### 341 **Pregnancy**

342 Women of childbearing potential should be advised to avoid becoming pregnant.

343 Imatinib mesylate was teratogenic in rats when administered during organogenesis at  
344 doses  $\geq 100$  mg/kg, approximately equal to the maximum clinical dose of 800 mg/day (based  
345 on body surface area). Teratogenic effects included exencephaly or encephalocele,  
346 absent/reduced frontal and absent parietal bones. Female rats administered doses  $\geq 45$  mg/kg  
347 (approximately one-half the maximum human dose of 800 mg/day, based on body surface  
348 area) also experienced significant post-implantation loss as evidenced by either early fetal  
349 resorption or stillbirths, nonviable pups and early pup mortality between postpartum days 0  
350 and 4. At doses higher than 100 mg/kg, total fetal loss was noted in all animals. Fetal loss was  
351 not seen at doses  $\leq 30$  mg/kg (one-third the maximum human dose of 800 mg).

352 Male and female rats were exposed *in utero* to a maternal imatinib mesylate dose of  
353 45 mg/kg (approximately one-half the maximum human dose of 800 mg) from day 6 of  
354 gestation and through milk during the lactation period. These animals then received no  
355 imatinib exposure for nearly 2 months. Body weights were reduced from birth until terminal  
356 sacrifice in these rats. Although fertility was not affected, fetal loss was seen when these male  
357 and female animals were then mated.

358 There are no adequate and well-controlled studies in pregnant women. If Gleevec®  
359 (imatinib mesylate) is used during pregnancy, or if the patient becomes pregnant while taking  
360 (receiving) Gleevec, the patient should be apprised of the potential hazard to the fetus.

## 361 PRECAUTIONS

### 362 General

#### 363 *Dermatologic Toxicities:*

364 Bullous dermatologic reactions, including erythema multiforme and Stevens Johnson  
365 syndrome, have been reported with use of Gleevec. In some cases reported during post-  
366 marketing surveillance, a recurrent dermatologic reaction was observed upon rechallenge.  
367 Several foreign post-marketing reports have described cases in which patients tolerated the  
368 reintroduction of Gleevec therapy after resolution or improvement of the bullous reaction. In  
369 these instances, Gleevec was resumed at a dose lower than that at which the reaction occurred  
370 and some patients also received concomitant treatment with corticosteroids or antihistamines.

371

372 ***Fluid Retention and Edema:*** Gleevec® (imatinib mesylate) is often associated with edema  
373 and occasionally serious fluid retention (see ADVERSE REACTIONS). Patients should be  
374 weighed and monitored regularly for signs and symptoms of fluid retention. An unexpected  
375 rapid weight gain should be carefully investigated and appropriate treatment provided. The  
376 probability of edema was increased with higher Gleevec dose and age >65 years in the CML  
377 studies. Severe superficial edema was reported in 0.9% of newly diagnosed CML patients  
378 taking Gleevec, and in 2%-6%[10] of other adult CML patients taking Gleevec. In addition,  
379 other severe fluid retention (e.g., pleural effusion, pericardial effusion, pulmonary edema, and  
380 ascites) events were reported in 2%-6% of other adult CML patients taking Gleevec [10].  
381 There have been post-marketing reports, including fatalities, of cerebral edema, increased  
382 intracranial pressure, and papilledema in patients with CML treated with Gleevec.

383 Severe superficial edema and severe fluid retention (pleural effusion, pulmonary  
384 edema and ascites) were reported in 1%-6% of patients taking Gleevec for GIST.

385 ***GI Irritation:*** Gleevec is sometimes associated with GI irritation. Gleevec should be taken  
386 with food and a large glass of water to minimize this problem.

387 ***Hemorrhage:*** In the newly diagnosed CML trial, 0.7% of patients had grade 3/4 hemorrhage.  
388 In the GIST clinical trial seven patients (5%), four in the 600-mg dose group and three in the  
389 400-mg dose group, had a total of eight events of CTC grade 3/4 - gastrointestinal (GI) bleeds  
390 (3 patients), intra-tumoral bleeds (3 patients) or both (1 patient). Gastrointestinal tumor sites  
391 may have been the source of GI bleeds.

392 ***Hematologic Toxicity:*** Treatment with Gleevec is associated with anemia, neutropenia, and  
393 thrombocytopenia. Complete blood counts should be performed weekly for the first month,  
394 biweekly for the second month, and periodically thereafter as clinically indicated (for example  
395 every 2-3 months). In CML, the occurrence of these cytopenias is dependent on the stage of  
396 disease and is more frequent in patients with accelerated phase CML or blast crisis than in  
397 patients with chronic phase CML. (See DOSAGE AND ADMINISTRATION.)

398 **Hepatotoxicity:** Hepatotoxicity, occasionally severe, may occur with Gleevec (see  
399 ADVERSE REACTIONS). Liver function (transaminases, bilirubin, and alkaline  
400 phosphatase) should be monitored before initiation of treatment and monthly or as clinically  
401 indicated. Laboratory abnormalities should be managed with interruption and/or dose  
402 reduction of the treatment with Gleevec. (See DOSAGE AND ADMINISTRATION.) Patients  
403 with hepatic impairment should be closely monitored because exposure to Gleevec may be  
404 increased. As there are no clinical studies of Gleevec in patients with impaired liver function,  
405 no specific advice concerning initial dosing adjustment can be given.

406 **Toxicities From Long-Term Use:** It is important to consider potential toxicities suggested by  
407 animal studies, specifically, *liver and kidney toxicity and immunosuppression*. Severe liver  
408 toxicity was observed in dogs treated for 2 weeks, with elevated liver enzymes, hepatocellular  
409 necrosis, bile duct necrosis, and bile duct hyperplasia. Renal toxicity was observed in  
410 monkeys treated for 2 weeks, with focal mineralization and dilation of the renal tubules and  
411 tubular nephrosis. Increased BUN and creatinine were observed in several of these animals.  
412 An increased rate of opportunistic infections was observed with chronic imatinib treatment in  
413 laboratory animal studies. In a 39-week monkey study, treatment with imatinib resulted in  
414 worsening of normally suppressed malarial infections in these animals. Lymphopenia was  
415 observed in animals (as in humans).

## 416 **Drug Interactions**

### 417 **Drugs that may alter imatinib plasma concentrations**

418 Drugs that may **increase** imatinib plasma concentrations:

419 Caution is recommended when administering Gleevec with inhibitors of the CYP3A4 family  
420 (e.g., ketoconazole, itraconazole, erythromycin, clarithromycin). Substances that inhibit the  
421 cytochrome P450 isoenzyme (CYP3A4) activity may decrease metabolism and increase  
422 imatinib concentrations. There is a significant increase in exposure to imatinib when Gleevec  
423 is coadministered with ketoconazole (CYP3A4 inhibitor).

424 Drugs that may **decrease** imatinib plasma concentrations:

425 Substances that are inducers of CYP3A4 activity may increase metabolism and decrease  
426 imatinib plasma concentrations. Co-medications that induce CYP3A4 (e.g., dexamethasone,  
427 phenytoin, carbamazepine, rifampin, phenobarbital or St. John's Wort) may significantly  
428 reduce exposure to Gleevec. Pretreatment of healthy volunteers with multiple doses of  
429 rifampin followed by a single dose of Gleevec, increased Gleevec oral-dose clearance by  
430 3.8-fold, which significantly ( $p < 0.05$ ) decreased mean  $C_{max}$  and  $AUC_{(0-\infty)}$ . In patients where  
431 rifampin or other CYP3A4 inducers are indicated, alternative therapeutic agents with less  
432 enzyme induction potential should be considered. (See CLINICAL PHARMACOLOGY and  
433 DOSAGE AND ADMINISTRATION.)

### 434 **Drugs that may have their plasma concentration altered by Gleevec**

435 Gleevec increases the mean  $C_{max}$  and AUC of simvastatin (CYP3A4 substrate) 2- and  
436 3.5-fold, respectively, suggesting an inhibition of the CYP3A4 by Gleevec. Particular caution  
437 is recommended when administering Gleevec with CYP3A4 substrates that have a narrow  
438 therapeutic window (e.g., cyclosporine or pimozone). Gleevec will increase plasma

439 concentration of other CYP3A4 metabolized drugs (e.g., triazolo-benzodiazepines,  
440 dihydropyridine calcium channel blockers, certain HMG-CoA reductase inhibitors, etc.).

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

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

#### 447 **Carcinogenesis, Mutagenesis, Impairment of Fertility**

448 Carcinogenicity studies have not been performed with imatinib mesylate.

449 Positive genotoxic effects were obtained for imatinib in an *in vitro* mammalian cell  
450 assay (Chinese hamster ovary) for clastogenicity (chromosome aberrations) in the presence of  
451 metabolic activation. Two intermediates of the manufacturing process, which are also present  
452 in the final product, are positive for mutagenesis in the Ames assay. One of these  
453 intermediates was also positive in the mouse lymphoma assay. Imatinib was not genotoxic  
454 when tested in an *in vitro* bacterial cell assay (Ames test), an *in vitro* mammalian cell assay  
455 (mouse lymphoma) and an *in vivo* rat micronucleus assay.

456 In a study of fertility, in male rats dosed for 70 days prior to mating, testicular and  
457 epididymal weights and percent motile sperm were decreased at 60 mg/kg, approximately  
458 three-fourths the maximum clinical dose of 800 mg/day, based on body surface area. This was  
459 not seen at doses  $\leq 20$  mg/kg (one-fourth the maximum human dose of 800 mg). When female  
460 rats were dosed 14 days prior to mating and through to gestational day 6, there was no effect  
461 on mating or on number of pregnant females.

462 In female rats dosed with imatinib mesylate at 45 mg/kg (approximately one-half the  
463 maximum human dose of 800 mg, based on body surface area) from gestational day 6 until  
464 the end of lactation, red vaginal discharge was noted on either gestational day 14 or 15.

#### 465 **Pregnancy**

466 ***Pregnancy Category D. (See WARNINGS.)***

#### 467 **Nursing Mothers**

468 It is not known whether imatinib mesylate or its metabolites are excreted in human milk.  
469 However, in lactating female rats administered 100 mg/kg, a dose approximately equal to the  
470 maximum clinical dose of 800 mg/day based on body surface area, imatinib and its  
471 metabolites were extensively excreted in milk. Concentration in milk was approximately  
472 three-fold higher than in plasma. It is estimated that approximately 1.5% of a maternal dose is  
473 excreted into milk, which is equivalent to a dose to the infant of 30% the maternal dose per  
474 unit body weight. Because many drugs are excreted in human milk and because of the  
475 potential for serious adverse reactions in nursing infants, women should be advised against  
476 breastfeeding while taking Gleevec.

**477 Pediatric Use**

478 Gleevec safety and efficacy have been demonstrated only in children with Ph+ chronic phase  
479 CML with recurrence after stem cell transplantation or resistance to interferon alpha therapy.  
480 There are no data in children under 3 years of age.

**481 Geriatric Use**

482 In the CML clinical studies, approximately 40% of patients were older than 60 years and 10%  
483 were older than 70 years. In the study of patients with newly diagnosed CML, 22% of patients  
484 were 60 years of age or older. No difference was observed in the safety profile in patients  
485 older than 65 years as compared to younger patients, with the exception of a higher frequency  
486 of edema. (See PRECAUTIONS.) The efficacy of Gleevec was similar in older and younger  
487 patients.

488 In the GIST study, 29% of patients were older than 60 years and 10% of patients were  
489 older than 70 years. No obvious differences in the safety or efficacy profile were noted in  
490 patients older than 65 years as compared to younger patients, but the small number of patients  
491 does not allow a formal analysis.

**492 ADVERSE REACTIONS****493 Chronic Myeloid Leukemia**

494 The majority of Gleevec-treated patients experienced adverse events at some time. Most  
495 events were of mild-to-moderate grade, but drug was discontinued for drug-related adverse  
496 events in 4% of patients in chronic phase, 5% in accelerated phase and 5% in blast crisis. [11]

497 The most frequently reported drug-related adverse events were edema, nausea and  
498 vomiting, muscle cramps, musculoskeletal pain, diarrhea and rash [12] (Table 4 for newly  
499 diagnosed CML, Table 5 for other CML patients). Edema was most frequently periorbital or  
500 in lower limbs and was managed with diuretics, other supportive measures, or by reducing the  
501 dose of Gleevec<sup>®</sup> (imatinib mesylate). (See DOSAGE AND ADMINISTRATION.) The  
502 frequency of severe superficial edema was 0.9%-6%.[13]

503 A variety of adverse events represent local or general fluid retention including pleural  
504 effusion, ascites, pulmonary edema and rapid weight gain with or without superficial edema.  
505 These events appear to be dose related, were more common in the blast crisis and accelerated  
506 phase studies (where the dose was 600 mg/day), and are more common in the elderly. These  
507 events were usually managed by interrupting Gleevec treatment and with diuretics or other  
508 appropriate supportive care measures. However, a few of these events may be serious or life  
509 threatening, and one patient with blast crisis died with pleural effusion, congestive heart  
510 failure, and renal failure.

511 Adverse events, regardless of relationship to study drug, that were reported in at least  
512 10% of the patients treated in the Gleevec studies are shown in Tables 4 and 5.

513 **Table 4 Adverse Experiences Reported in Newly Diagnosed CML Clinical Trial**  
 514 **(≥10% of all patients)<sup>(1)</sup>**

515 516 517 <b>Preferred Term</b>	<b>All Grades</b>		<b>CTC Grades 3/4</b>	
	<b>Gleevec®</b> <b>N=551 (%)</b>	<b>IFN+Ara-C</b> <b>N=533 (%)</b>	<b>Gleevec™</b> <b>N=551 (%)</b>	<b>IFN+Ara-C</b> <b>N=533 (%)</b>
518 Fluid Retention	54.1	10.1	0.9	0.9
519 - Superficial Edema	53.2	8.8	0.9	0.4
520 - Other Fluid				
521 Retention Events	3.4	1.5	0	0.6
522 Nausea	42.5	60.8	0.4	5.1
523 Muscle Cramps	35.4	9.9	1.1	0.2
524 Musculoskeletal Pain	33.6	40.5	2.7	7.7
525 Rash	31.9	25.0	2.0	2.1
526 Fatigue	30.7	64.7	1.1	24.0
527 Diarrhea	30.3	40.9	1.3	3.2
528 Headache	28.5	41.8	0.4	3.2
529 Joint Pain	26.7	38.3	2.2	6.8
530 Abdominal Pain	23.4	22.9	2.0	3.6
531 Myalgia	20.9	38.6	1.5	8.1
532 Nasopharyngitis	19.2	7.7	0	0.2
533 Hemorrhage	18.9	19.9	0.7	1.3
534 Dyspepsia	15.1	9.0	0	0.8
535 Vomiting	14.7	26.6	0.9	3.4
536 Pharyngolaryngeal Pain	14.2	11.4	0.2	0
537 Dizziness	13.2	23.1	0.5	3.4
538 Cough	12.5	21.6	0.2	0.6
539 Upper Respiratory				
540 Tract Infection	12.5	7.9	0.2	0.4
541 Pyrexia	11.8	38.6	0.5	2.8
542 Weight Increased	11.6	1.5	0.7	0.2
543 Insomnia	11.4	18.4	0	2.3

544 <sup>(1)</sup> All adverse events occurring in ≥10% of patients are listed regardless of suspected relationship to  
 545 treatment.

546 **Table 5** Adverse Experiences Reported in Other CML Clinical Trials ( $\geq 10\%$  of all patients  
 547 in any trial)<sup>(1)</sup> [14]

548 549 550 551 552 553	Preferred Term	Myeloid Blast Crisis (n= 260) %		Accelerated Phase (n=235) %		Chronic Phase, IFN Failure (n=532) %	
		All Grades	Grade 3/4	All Grades	Grade 3/4	All Grades	Grade 3/4
554	Fluid Retention	72	11	76	6	69	4
555	- Superficial Edema	66	6	74	3	67	2
556	- Other Fluid Retention Events <sup>(2)</sup>	22	6	15	4	7	2
557	Nausea	71	5	73	5	63	3
558	Muscle Cramps	28	1	47	0.4	62	2
559	Vomiting	54	4	58	3	36	2
560	Diarrhea	43	4	57	5	48	3
561	Hemorrhage	53	19	49	11	30	2
562	- CNS Hemorrhage	9	7	3	3	2	1
563	- Gastrointestinal Hemorrhage	8	4	6	5	2	0.4
564	Musculoskeletal Pain	42	9	49	9	38	2
565	Fatigue	30	4	46	4	48	1
566	Skin Rash	36	5	47	5	47	3
567	Pyrexia	41	7	41	8	21	2
568	Arthralgia	25	5	34	6	40	1
569	Headache	27	5	32	2	36	0.6
570	Abdominal Pain	30	6	33	4	32	1
571	Weight Increased	5	1	17	5	32	7
572	Cough	14	0.8	27	0.9	20	0
573	Dyspepsia	12	0	22	0	27	0
574	Myalgia	9	0	24	2	27	0.2
575	Nasopharyngitis	10	0	17	0	22	0.2
576	Asthenia	18	5	21	5	15	0.2
577	Dyspnea	15	4	21	7	12	0.9
578	Upper Respiratory Tract Infection	3	0	12	0.4	19	0
579	Anorexia	14	2	17	2	7	0
580	Night sweats	13	0.8	17	1	14	0.2
581	Constipation	16	2	16	0.9	9	0.4
582	Dizziness	12	0.4	13	0	16	0.2
583	Pharyngitis	10	0	12	0	15	0
584	Insomnia	10	0	14	0	14	0.2
585	Pruritus	8	1	14	0.9	14	0.8
586	Hypokalemia	13	4	9	2	6	0.8
587	Pneumonia	13	7	10	7	4	1
588	Anxiety	8	0.8	12	0	8	0.4
589	Liver Toxicity	10	5	12	6	6	3
590	Rigors	10	0	12	0.4	10	0
591	Chest Pain	7	2	10	0.4	11	0.8
592	Influenza	0.8	0.4	6	0	11	0.2
593	Sinusitis	4	0.4	11	0.4	9	0.4

594 <sup>(1)</sup> All adverse events occurring in  $\geq 10\%$  of patients are listed regardless of suspected relationship to  
 595 treatment.

596 <sup>(2)</sup> Other fluid retention events include pleural effusion, ascites, pulmonary edema, pericardial effusion,  
 597 anasarca, edema aggravated, and fluid retention not otherwise specified.



## 598 **Hematologic Toxicity**

599 Cytopenias, and particularly neutropenia and thrombocytopenia, were a consistent finding in  
600 all studies, with a higher frequency at doses  $\geq 750$  mg (Phase 1 study). However, the  
601 occurrence of cytopenias in CML patients was also dependent on the stage of the disease.

602 In patients with newly diagnosed CML, cytopenias were less frequent than in the other  
603 CML patients (see Tables 6 and 7). The frequency of grade 3 or 4 neutropenia and  
604 thrombocytopenia was between 2- and 3-fold higher in blast crisis and accelerated phase  
605 compared to chronic phase (see Tables 6 and 7). The median duration of the neutropenic and  
606 thrombocytopenic episodes varied from 2 to 3 weeks, and from 2 to 4 weeks, respectively.

607 These events can usually be managed with either a reduction of the dose or an  
608 interruption of treatment with Gleevec, but in rare cases require permanent discontinuation of  
609 treatment.

## 610 **Hepatotoxicity**

611 Severe elevation of transaminases or bilirubin occurred in 3%-6%<sup>[15]</sup> (see Table 5) and were  
612 usually managed with dose reduction or interruption (the median duration of these episodes  
613 was approximately one week). Treatment was discontinued permanently because of liver  
614 laboratory abnormalities in less than 1%<sup>[16]</sup> of patients. However, one patient, who was  
615 taking acetaminophen regularly for fever, died of acute liver failure.

## 616 **Adverse Reactions in Pediatric Population**

617 The overall safety profile of pediatric patients treated with Gleevec in 39 children studied was  
618 similar to that found in studies with adult patients, except that musculoskeletal pain was less  
619 frequent (20.5%) and peripheral edema was not reported.

## 620 **Adverse Effects in Other Subpopulations**

621 In older patients ( $\geq 65$  years old), with the exception of edema, where it was more frequent,  
622 there was no evidence of an increase in the incidence or severity of adverse events. In women  
623 there was an increase in the frequency of neutropenia, as well as grade 1/2 superficial edema,  
624 headache, nausea, rigors, vomiting, rash, and fatigue. No differences were seen related to race  
625 but the subsets were too small for proper evaluation.

626 **Table 6 Lab Abnormalities in Newly Diagnosed CML Trial**

	Gleevec® N=551 %		IFN+Ara-C N=533 %	
CTC Grades	Grade 3	Grade 4	Grade 3	Grade 4
<b>Hematology Parameters</b>				
- Neutropenia*	11.4	2.2	20.3	4.3
- Thrombocytopenia*	6.9	0.2	15.8	0.6
- Anemia	2.7	0.4	4.1	0.2
<b>Biochemistry Parameters</b>				
- Elevated Creatinine	0	0	0.4	0
- Elevated Bilirubin	0.2	0.5	0.2	0
- Elevated Alkaline Phosphatase	0.2	0	0.8	0
- Elevated SGOT (AST)	2.9	0.2	3.8	0.4
- Elevated SGPT (ALT)	3.1	0.4	5.6	0

642 \*p&lt;0.001 (difference in grade 3 plus 4 abnormalities between the two treatment groups)

643 **Table 7 Lab Abnormalities in Other CML Clinical Trials [17]**

	Myeloid Blast Crisis (n=260) 600 mg n=223 400 mg n=37 %		Accelerated Phase (n=235) 600 mg n=158 400 mg n=77 %		Chronic Phase, IFN Failure (n=532) 400 mg %	
CTC Grades	Grade 3	Grade 4	Grade 3	Grade 4	Grade 3	Grade 4
<b>Hematology Parameters</b>						
- Neutropenia	16	48	23	36	27	9
- Thrombocytopenia	30	33	31	13	21	<1
- Anemia	42	11	34	7	6	1
<b>Biochemistry Parameters</b>						
- Elevated Creatinine	1.5	0	1.3	0	0.2	0
- Elevated Bilirubin	3.8	0	2.1	0	0.6	0
- Elevated Alkaline Phosphatase	4.6	0	5.5	0.4	0.2	0
- Elevated SGOT (AST)	1.9	0	3.0	0	2.3	0
- Elevated SGPT (ALT)	2.3	0.4	4.3	0	2.1	0

663 CTC grades: neutropenia (grade 3  $\geq 0.5-1.0 \times 10^9/L$ , grade 4  $< 0.5 \times 10^9/L$ ), thrombocytopenia (grade 3  
664  $\geq 10-50 \times 10^9/L$ , grade 4  $< 10 \times 10^9/L$ ), anemia (hemoglobin  $\geq 65-80$  g/L, grade 4  $< 65$  g/L), elevated  
665 creatinine (grade 3  $> 3-6$  x upper limit normal range (ULN), grade 4  $> 6$  x ULN), elevated bilirubin (grade  
666 3  $> 3-10$  x ULN, grade 4  $> 10$  x ULN), elevated alkaline phosphatase (grade 3  $> 5-20$  x ULN, grade 4  $> 20$   
667 x ULN), elevated SGOT or SGPT (grade 3  $> 5-20$  x ULN, grade 4  $> 20$  x ULN)

668 **Gastrointestinal Stromal Tumors**

669 The majority of Gleevec-treated patients experienced adverse events at some time. The most  
670 frequently reported adverse events were edema, nausea, diarrhea, abdominal pain, muscle  
671 cramps, fatigue, and rash. Most events were of mild-to-moderate severity. Drug was

672 discontinued for adverse events in 6 patients (8%) in both dose levels studied. Superficial  
 673 edema, most frequently periorbital or lower extremity edema, was managed with diuretics,  
 674 other supportive measures, or by reducing the dose of Gleevec<sup>®</sup> (imatinib mesylate).  
 675 (See DOSAGE AND ADMINISTRATION.) Severe (CTC grade 3/4) superficial edema was  
 676 observed in 3 patients (2%), including face edema in one patient. Grade 3/4 pleural effusion  
 677 or ascites was observed in 3 patients (2%).

678 Adverse events, regardless of relationship to study drug, that were reported in at least  
 679 10% of the patients treated with Gleevec are shown in Table 8. No major differences were  
 680 seen in the severity of adverse events between the 400-mg or 600-mg treatment groups,  
 681 although overall incidence of diarrhea, muscle cramps, headache, dermatitis, and edema was  
 682 somewhat higher in the 600-mg treatment group.

683 **Table 8 Adverse Experiences Reported in GIST Trial (≥10% of all patients at either**  
 684 **dose)<sup>(1)</sup>**

685 686 687 688 689	690 691 692 693 694 695 696 697 698 699 700 701 702 703 704 705 706 707 708 709 710 711 712 713	All CTC Grades		CTC Grade 3/4	
		Initial dose (mg/day)		Initial dose (mg/day)	
		400 mg (n=73)	600 mg (n=74)	400 mg (n=73)	600 mg (n=74)
Preferred Term		%	%	%	%
Fluid Retention		71	76	6	3
- Superficial Edema		71	76	4	0
- Pleural Effusion or Ascites		6	4	1	3
Diarrhea		56	60	1	4
Nausea		53	56	3	3
Fatigue		33	38	1	0
Muscle Cramps		30	41	0	0
Abdominal Pain		37	37	7	3
Skin Rash		26	38	3	3
Headache		25	35	0	0
Vomiting		22	23	1	3
Musculoskeletal Pain		19	11	3	0
Flatulence		16	23	0	0
Any Hemorrhage		18	19	5	8
- Tumor Hemorrhage		1	4	1	4
- Cerebral Hemorrhage		1	0	1	0
- GI Tract Hemorrhage		6	4	4	1
Nasopharyngitis		12	14	0	0
Pyrexia		12	5	0	0
Insomnia		11	11	0	0
Back Pain		11	10	1	0
Lacrimation Increased		6	11	0	0
Upper Respiratory Tract Infection		6	11	0	0
Taste Disturbance		1	14	0	0

714 <sup>(1)</sup> All adverse events occurring in ≥10% of patients are listed regardless of suspected relationship to  
 715 treatment.

716 Clinically relevant or severe abnormalities of routine hematologic or biochemistry  
717 laboratory values are presented in Table 9.

718 **Table 9 Laboratory Abnormalities in GIST Trial**

	400 mg (n=73) %		600 mg (n=74) %	
<b>CTC Grades</b>	<b>Grade 3</b>	<b>Grade 4</b>	<b>Grade 3</b>	<b>Grade 4</b>
<b>Hematology Parameters</b>				
724 - Anemia	3	0	4	1
725 - Thrombocytopenia	0	0	1	0
726 - Neutropenia	3	3	5	4
<b>Biochemistry Parameters</b>				
728 - Elevated Creatinine	0	1	3	0
729 - Reduced Albumin	3	0	4	0
730 - Elevated Bilirubin	1	0	1	3
731 - Elevated Alkaline Phosphatase	0	0	1	0
732 - Elevated SGOT (AST)	3	0	1	1
733 - Elevated SGPT (ALT)	3	0	4	0

734 CTC grades: neutropenia (grade 3  $\geq 0.5-1.0 \times 10^9/L$ , grade 4  $< 0.5 \times 10^9/L$ ), thrombocytopenia (grade 3  
735  $\geq 10 - 50 \times 10^9/L$ , grade 4  $< 10 \times 10^9/L$ ), anemia (grade 3  $\geq 65-80$  g/L, grade 4  $< 65$  g/L), elevated  
736 creatinine (grade 3  $> 3-6$  x upper limit normal range (ULN), grade 4  $> 6$  x ULN), elevated bilirubin (grade  
737 3  $> 3-10$  x ULN, grade 4  $> 10$  x ULN), elevated alkaline phosphatase, SGOT or SGPT (grade 3  $> 5-20$  x  
738 ULN, grade 4  $> 20$  x ULN), albumin (grade 3  $< 20$  g/L)

### 739 **Additional Data From Multiple Clinical Trials**

740  
741 The following less common (estimated 1%-10%), infrequent (estimated 0.1%-1%), and rare  
742 (estimated less than 0.1%) adverse events have been reported during clinical trials of Gleevec.  
743 These events are included based on clinical relevance.

744  
745 **Cardiovascular:** *Infrequent:* cardiac failure, tachycardia, hypertension, hypotension, flushing,  
746 peripheral coldness

747  
748 **Clinical Laboratory Tests:** *Infrequent:* blood CPK increased, blood LDH increased

749  
750 **Dermatologic:** *Less common:* dry skin, alopecia *Infrequent:* exfoliative dermatitis, bullous  
751 eruption, nail disorder, skin pigmentation changes, photosensitivity reaction, purpura *Rare:*  
752 vesicular rash, Stevens-Johnson syndrome, acute generalized exanthematous pustulosis

753  
754 **Digestive:** *Less common:* abdominal distension, gastroesophageal reflux, mouth ulceration  
755 *Infrequent:* gastric ulcer, gastroenteritis, gastritis *Rare:* colitis

756  
757 **Hematologic:** *Infrequent:* pancytopenia *Rare:* aplastic anemia

758  
759 **Hypersensitivity:** *Rare:* angioedema  
760

761 **Infections:** *Infrequent:* sepsis, herpes simplex, herpes zoster  
762  
763 **Metabolic and Nutritional:** *Infrequent:* hypophosphatemia, dehydration, gout, appetite  
764 disturbances, weight decreased *Rare:* hyperkalemia, hyponatremia  
765  
766 **Musculoskeletal:** *Less common:* joint swelling *Infrequent:* sciatica, joint and muscle stiffness  
767  
768 **Nervous System/Psychiatric:** *Less common:* paresthesia *Infrequent:* depression, anxiety,  
769 syncope, peripheral neuropathy, somnolence, migraine, memory impairment *Rare:* increased  
770 intracranial pressure, cerebral edema (including fatalities)  
771  
772 **Renal:** *Infrequent:* renal failure, urinary frequency, hematuria  
773  
774 **Reproductive:** *Infrequent:* breast enlargement, menorrhagia, sexual dysfunction  
775  
776 **Respiratory:** *Rare:* interstitial pneumonitis, pulmonary fibrosis  
777  
778 **Special Senses:** *Less common:* conjunctivitis, vision blurred *Infrequent:* conjunctival  
779 hemorrhage, dry eye, vertigo, tinnitus *Rare:* macular edema, papilledema, retinal hemorrhage  
780  
781

## 782 **OVERDOSAGE**

783 Experience with doses greater than 800 mg is limited. In the event of overdose, the patient  
784 should be observed and appropriate supportive treatment given. An oral dose of  
785 1200 mg/m<sup>2</sup>/day, approximately 2.5 times the human dose of 800 mg, based on body surface  
786 area, was not lethal to rats following 14 days of administration. A dose of 3600 mg/m<sup>2</sup>/day,  
787 approximately 7.5 times the human dose of 800 mg, was lethal to rats after 7-10  
788 administrations, due to general deterioration of the animals with secondary degenerative  
789 histological changes in many tissues.

## 790 **DOSAGE AND ADMINISTRATION**

791 Therapy should be initiated by a physician experienced in the treatment of patients with  
792 chronic myeloid leukemia or gastrointestinal stromal tumors.

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

799 The prescribed dose should be administered orally, with a meal and a large glass of  
800 water. Doses of 400 mg or 600 mg should be administered once daily, whereas a dose of  
801 800 mg should be administered as 400 mg twice a day.

802 In children, Gleevec treatment can be given as a once daily dose or alternatively the  
803 daily dose may be split into two - once in the morning and once in the evening. There is no  
804 experience with Gleevec treatment in children under 3 years of age.

805 For patients unable to swallow the film-coated tablets, the tablets may be dispersed in  
806 a glass of water or apple juice. The required number of tablets should be placed in the  
807 appropriate volume of beverage (approximately 50 mL for a 100-mg tablet, and 200 mL for a  
808 400-mg tablet) and stirred with a spoon. The suspension should be administered immediately  
809 after complete disintegration of the tablet(s).

810 Treatment may be continued as long as there is no evidence of progressive disease or  
811 unacceptable toxicity.

812 In CML, a dose increase from 400 mg to 600 mg in adult patients with chronic phase  
813 disease, or from 600 mg to 800 mg (given as 400 mg twice daily) in adult patients in  
814 accelerated phase or blast crisis may be considered in the absence of severe adverse drug  
815 reaction and severe non-leukemia related neutropenia or thrombocytopenia in the following  
816 circumstances: disease progression (at any time); failure to achieve a satisfactory  
817 hematologic response after at least 3 months of treatment; failure to achieve a cytogenetic  
818 response after 6-12 months of treatment; or loss of a previously achieved hematologic or  
819 cytogenetic response. In children with chronic phase CML, daily doses can be increased under  
820 circumstances similar to those leading to an increase in adult chronic phase disease, from  
821 260 mg/m<sup>2</sup>/day to 340 mg/m<sup>2</sup>/day, as clinically indicated.

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

## 825 **Dose Adjustment for Hepatotoxicity and Other Non-Hematologic Adverse** 826 **Reactions**

827 If a severe non-hematologic adverse reaction develops (such as severe hepatotoxicity or  
828 severe fluid retention), Gleevec should be withheld until the event has resolved. Thereafter,  
829 treatment can be resumed as appropriate depending on the initial severity of the event.

830 If elevations in bilirubin >3 x institutional upper limit of normal (IULN) or in liver  
831 transaminases >5 x IULN occur, Gleevec should be withheld until bilirubin levels have  
832 returned to a <1.5 x IULN and transaminase levels to <2.5 x IULN. In adults, treatment with  
833 Gleevec may then be continued at a reduced daily dose (i.e., 400 mg to 300 mg or 600 mg to  
834 400 mg). In children, daily doses can be reduced under the same circumstances from  
835 260 mg/m<sup>2</sup>/day to 200 mg/m<sup>2</sup>/day or from 340 mg/m<sup>2</sup>/day to 260 mg/m<sup>2</sup>/day, respectively.

## 836 **Dose Adjustment for Hematologic Adverse Reactions**

837 Dose reduction or treatment interruptions for severe neutropenia and thrombocytopenia are  
838 recommended as indicated in Table 10.

<b>Table 10 Dose Adjustments for Neutropenia and Thrombocytopenia</b>			
839	<b>Table 10</b>	<b>Dose Adjustments for Neutropenia and Thrombocytopenia</b>	
840	Chronic Phase CML	ANC <1.0 x 10 <sup>9</sup> /L	1. Stop Gleevec until ANC
841	(starting dose 400mg <sup>1</sup> )	and/or	≥1.5 x 10 <sup>9</sup> /L and
842		Platelets <50 x 10 <sup>9</sup> /L	platelets ≥75 x 10 <sup>9</sup> /L
843	or GIST		2. Resume treatment with
844	(starting dose either		Gleevec at the original
845	400 mg or 600 mg)		starting dose of 400 mg <sup>1</sup>
846			or 600 mg
847			3. If recurrence of ANC <1.0 x
848			10 <sup>9</sup> /L and/or platelets <50 x
849			10 <sup>9</sup> /L, repeat step 1 and
850			resume Gleevec at a reduced
851			dose (300 mg <sup>2</sup> if starting
852			dose was 400 mg <sup>1</sup> , 400 mg if
853			starting dose was 600 mg)
854	Accelerated Phase	<sup>3</sup> ANC <0.5 x 10 <sup>9</sup> /L	1. Check if cytopenia is
855	CML and Blast Crisis	and/or	related to leukemia
856	(starting dose 600 mg)	Platelets <10 x 10 <sup>9</sup> /L	(marrow aspirate or biopsy)
857			2. If cytopenia is unrelated to
858			leukemia, reduce dose of
859			Gleevec to 400 mg
860			3. If cytopenia persist 2 weeks,
861			reduce further to 300 mg
862			4. If cytopenia persist 4 weeks
863			and is still unrelated to
864			leukemia, stop Gleevec until
865			ANC ≥1 x 10 <sup>9</sup> /L and platelets
866			≥20 x 10 <sup>9</sup> /L and then resume
867			treatment at 300 mg.
868	<sup>1</sup> or 260 mg/m <sup>2</sup> in children		
869	<sup>2</sup> or 200 mg/m <sup>2</sup> in children		
870	<sup>3</sup> occurring after at least 1 month of treatment		

## 871 HOW SUPPLIED

872 Each film-coated tablet contains 100 mg or 400 mg of imatinib free base.

### 873 100 mg Tablets

874 Very dark yellow to brownish orange film-coated tablets, round, biconvex with bevelled  
875 edges debossed with “NVR” on one side and “SA” with score on the other side.

876 Bottles of 100 tablets .....NDC 0078-0401-05

### 877 400 mg Tablets

878 Very dark yellow to brownish orange film-coated tablets, ovaloid, biconvex with bevelled  
879 edges, debossed with “NVR” on one side and “SL” on the other side.

880 Bottles of 30 tablets .....NDC 0078-0402-15

881 **Storage**

882 Store at 25 °C (77 °F); excursions permitted to 15 °C-30 °C (59 °F-86 °F) [see USP  
883 Controlled Room Temperature]. Protect from moisture.

884 Dispense in a tight container, USP.

885 T200

886 REV: Printed in U.S.A.

887  **NOVARTIS**

888

889 Manufactured by:  
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