

4 **Gleevec<sup>®</sup>**  
5 **(imatinib mesylate)**

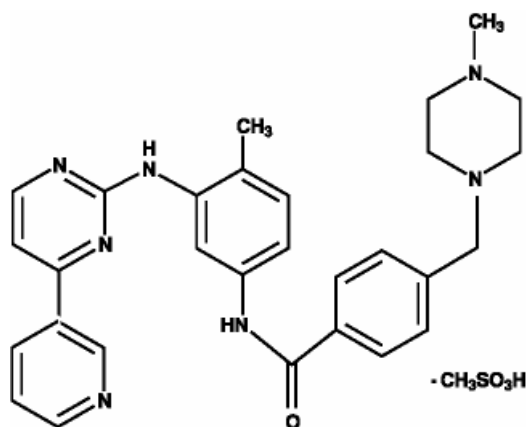
6 **Tablets**

7 **Rx only**

8 **Prescribing Information**

9 **DESCRIPTION**

10 Gleevec<sup>®</sup> (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 is  
43 well absorbed after oral administration with C<sub>max</sub> 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  $\leq$  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  $\mu$ M, 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*

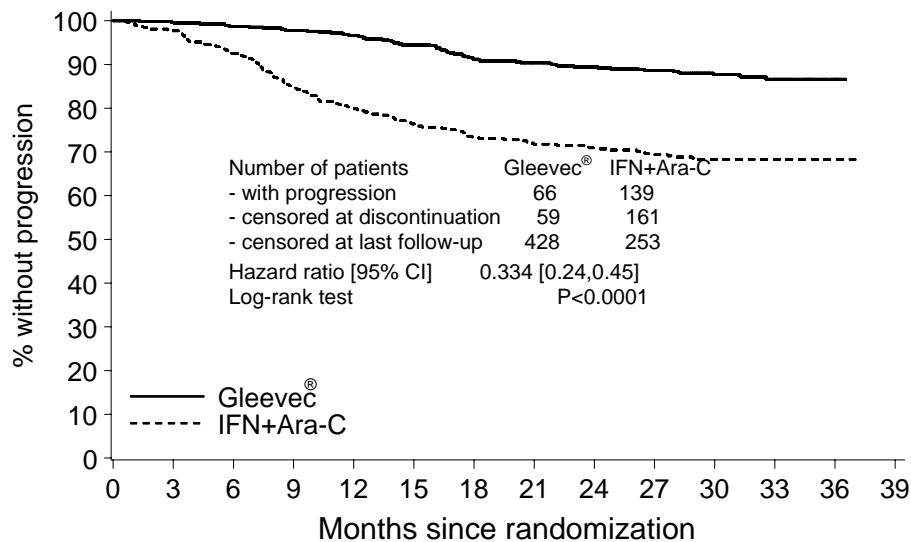
106 An open-label, multicenter, international randomized Phase 3 study has been conducted in  
107 patients with newly diagnosed Philadelphia chromosome positive (Ph+) chronic myeloid  
108 leukemia (CML) in chronic phase. This study compared treatment with either single-agent  
109 Gleevec<sup>®</sup> (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  $\geq$ 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 31  
122 and 30 months for Gleevec and IFN, respectively, 79% of patients randomized to Gleevec  
123 were still receiving first-line treatment. Due to discontinuations and cross-overs, only 7% of  
124 patients randomized to IFN were still on first-line treatment. In the IFN arm, withdrawal of  
125 consent (13.6%) 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 (25.1%).

128 The primary efficacy endpoint of the study was progression-free survival (PFS).  
129 Progression was defined as any of the following events: progression to accelerated phase or  
130 blast crisis, death, loss of CHR or MCyR, or in patients not achieving a CHR an increasing  
131 WBC despite appropriate therapeutic management. The protocol specified that the  
132 progression analysis would compare the intent to treat (ITT) population: patients randomized  
133 to receive Gleevec were compared with patients randomized to receive interferon. Patients  
134 that crossed over prior to progression were not censored at the time of cross-over, and events  
135 that occurred in these patients following cross-over were attributed to the original randomized  
136 treatment.. The estimated rate of progression-free survival at 30 months in the ITT population  
137 was 87.8% in the Gleevec arm and 68.3% in the IFN arm ( $p < 0.001$ ), (Figure 1). The estimated  
138 rate of patients free of progression to accelerated phase (AP) or blast crisis (BC) at 30 months  
139 was 94.8% in the Gleevec arm compared to 89.6%, ( $p = 0.0016$ ) in the IFN arm, (Figure 2.)  
140 There were 33 and 46 deaths reported in the Gleevec and IFN arm, respectively, with an  
141 estimated 30-month survival rate of 94.6% and 91.6% respectively (differences not  
142 significant). The probability of remaining progression-free at 30 months was 100% for  
143 patients who were in complete cytogenetic response with major molecular response ( $\geq$ 3-log  
144 reduction in bcr-abl transcripts as measured by quantitative reverse transcriptase polymerase  
145 chain reaction) at 12 months, compared to 93% for patients in complete cytogenetic response

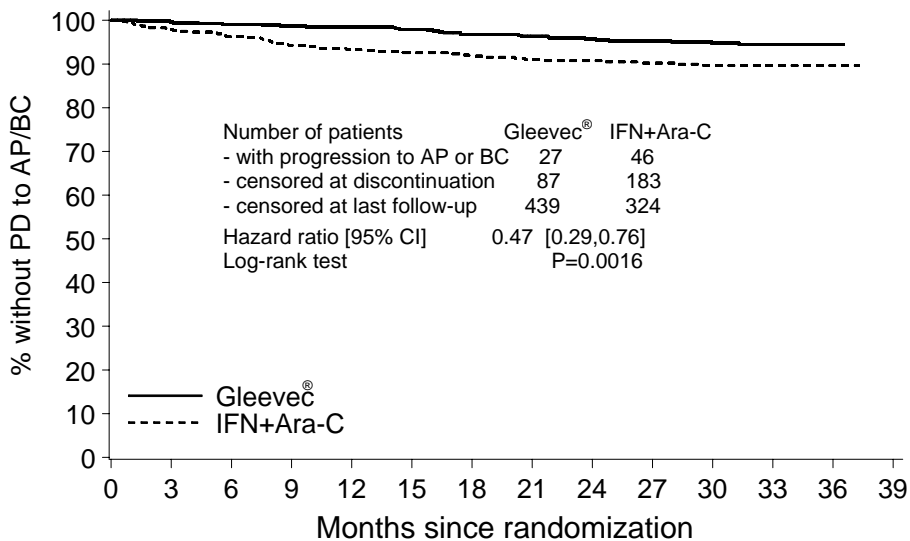
146 but without a major molecular response, and 82% in patients who were not in complete  
 147 cytogenetic response at this time point ( $p < 0.001$ ).

**Figure 1 Time to Progression (ITT)**



148  
 149  
 150

**Figure 2 Time to Progression to AP or BC (ITT)**



151  
 152

153 Major cytogenetic response, hematologic response, evaluation of minimal residual  
 154 disease (molecular response), time to accelerated phase or blast crisis and survival were main  
 155 secondary endpoints. Response data are shown in Table 1. Complete hematologic response,  
 156 major cytogenetic response and complete cytogenetic response were also statistically  
 157 significantly higher in the Gleevec arm compared to the IFN + Ara-C arm.

| Table 1 Response in Newly Diagnosed CML Study (First-Line) (30-month data)   |                |                  |                               |
|--|----------------|------------------|-------------------------------|
|  | Gleevec®       | IFN+Ara-C        |                               |
| (Best Response Rate)   | n=553          | n=553            |                               |
| <b>Hematologic Response<sup>1</sup></b>  |                |                  |                               |
| CHR Rate n (%)   | 527 (95.3%)*   | 308 (55.7%)*     |                               |
| [95% CI]   | [93.2%, 96.9%] | [51.4%, 59.9%]   |                               |
| <b>Cytogenetic Response<sup>2</sup></b>  |                |                  |                               |
| Major Cytogenetic Response n (%)   | 461 (83.4%)*   | 90 (16.3%)*      |                               |
| [95% CI]   | [80.0%, 86.4%] | [13.3%, 19.6%]   |                               |
| Unconfirmed <sup>3</sup>   | 87.2%*         | 23.0%*           |                               |
| Complete Cytogenetic Response n (%)  | 378 (68.4%)*   | 30(5.4%)*        |                               |
| Unconfirmed <sup>3</sup>   | 78.8%*         | 10.7%*           |                               |
| <b>Molecular response<sup>4</sup></b>  |                |                  |                               |
| Major response at 12 months (%)  | 40%*           | 2%*              |                               |
| Major response at 24 months (%)  | 54%*           | NA <sup>5*</sup> | p<0.001, Fischer's exact test |
| <sup>1</sup> <b>Hematologic response criteria (all responses to be confirmed after ≥4 weeks):</b>  |                |                  |                               |
| WBC<10 x 10 <sup>9</sup> /L, platelet <450 x 10 <sup>9</sup> /L, myelocyte + metamyelocyte <5% in blood, no blasts and promyelocytes in blood, basophils <20%, no extramedullary involvement.  |                |                  |                               |
| <sup>2</sup> <b>Cytogenetic response criteria (confirmed after ≥4 weeks):</b> complete (0% Ph+ metaphases). or partial (1%-35%). A major response (0%-35%) combines both complete and partial responses.   |                |                  |                               |
| <sup>3</sup> Unconfirmed cytogenetic response is based on a single bone marrow cytogenetic evaluation, therefore unconfirmed complete or partial cytogenetic responses might have had a lesser cytogenetic response on a subsequent bone marrow evaluation.                    |                |                  |                               |
| <sup>4</sup> <b>Major molecular response criteria:</b> in the peripheral blood, after 12 months of therapy, reduction of ≥3 logarithms in the amount of BCR-ABL transcripts (measured by real-time quantitative reverse transcriptase PCR assay) over a standardized baseline. |                |                  |                               |
| <sup>5</sup> Not Applicable: insufficient data, only two patients available with samples   |                |                  |                               |

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

### 193 **Late Chronic Phase CML and Advanced Stage CML**

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

### 199 **Chronic Phase, Prior Interferon-Treatment**

200 532 patients were treated at a starting dose of 400 mg; dose escalation to 600 mg was allowed.  
 201 The patients were distributed in three main categories according to their response to prior  
 202 interferon: failure to achieve (within 6 months), or loss of a complete hematologic response

203 (29%), failure to achieve (within 1 year) or loss of a major cytogenetic response (35%), or  
204 intolerance to interferon (36%). Patients had received a median of 14 months of prior IFN  
205 therapy at doses  $\geq 25 \times 10^6$  IU/week and were all in late chronic phase, with a median time  
206 from diagnosis of 32 months. Effectiveness was evaluated on the basis of the rate of  
207 hematologic response and by bone marrow exams to assess the rate of major cytogenetic  
208 response (up to 35% Ph+ metaphases) or complete cytogenetic response (0% Ph+  
209 metaphases). Median duration of treatment was 29 months with 81% of patients treated for  
210  $\geq 24$  months (maximum = 31.5 months). Efficacy results are reported in Table 2. Confirmed  
211 major cytogenetic response rates were higher in patients with IFN intolerance (66%) and  
212 cytogenetic failure (64%), than in patients with hematologic failure (47%). Hematologic  
213 response was achieved in 98% of patients with cytogenetic failure, 94% of patients with  
214 hematologic failure, and 92% of IFN-intolerant patients.

### 215 **Accelerated Phase**

216 235 patients with accelerated phase disease were enrolled. These patients met one or more of  
217 the following criteria:  $\geq 15\%$ - $<30\%$  blasts in PB or BM;  $\geq 30\%$  blasts + promyelocytes in PB  
218 or BM;  $\geq 20\%$  basophils in PB; and  $<100 \times 10^9/L$  platelets. The first 77 patients were started at  
219 400 mg, with the remaining 158 patients starting at 600 mg.

220 Effectiveness was evaluated primarily on the basis of the rate of hematologic response,  
221 reported as either complete hematologic response, no evidence of leukemia (i.e., clearance of  
222 blasts from the marrow and the blood, but without a full peripheral blood recovery as for  
223 complete responses), or return to chronic phase CML. Cytogenetic responses were also  
224 evaluated. Median duration of treatment was 18 months with 45% of patients treated for  $\geq 24$   
225 months (maximum = 35 months). Efficacy results are reported in Table 2. Response rates in  
226 accelerated phase CML were higher for the 600-mg dose group than for the 400-mg group:  
227 hematologic response (75% vs. 64%), confirmed and unconfirmed major cytogenetic response  
228 (31% vs. 19%).

### 229 **Myeloid Blast Crisis**

230 260 patients with myeloid blast crisis were enrolled. These patients had  $\geq 30\%$  blasts in PB or  
231 BM and/or extramedullary involvement other than spleen or liver; 95 (37%) had received  
232 prior chemotherapy for treatment of either accelerated phase or blast crisis (“pretreated  
233 patients”) whereas 165 (63%) had not (“untreated patients”). The first 37 patients were started  
234 at 400 mg; the remaining 223 patients were started at 600 mg.

235 Effectiveness was evaluated primarily on the basis of rate of hematologic response,  
236 reported as either complete hematologic response, no evidence of leukemia, or return to  
237 chronic phase CML using the same criteria as for the study in accelerated phase. Cytogenetic  
238 responses were also assessed. Median duration of treatment was 4 months with 21% of  
239 patients treated for  $\geq 12$  months and 10% for  $\geq 24$  months (maximum = 35 months). Efficacy  
240 results are reported in Table 2. The hematologic response rate was higher in untreated patients  
241 than in treated patients (36% vs. 22%, respectively) and in the group receiving an initial dose  
242 of 600 mg rather than 400 mg (33% vs. 16%). The confirmed and unconfirmed major  
243 cytogenetic response rate was also higher for the 600-mg dose group than for the 400 mg  
244 group (17% vs. 8%).

245 **Table 2**            **Response in CML Studies**

| 246 |   | <b>Chronic Phase</b>                    | <b>Accelerated</b>     | <b>Myeloid Blast</b>   |
|-----|---|---|------------------------|------------------------|
| 247 |   | <b>IFN Failure</b>                      | <b>Phase</b>           | <b>Crisis</b>          |
| 248 |   | <b>(n=532)</b>                          | <b>(n=235)</b>         | <b>(n=260)</b>         |
| 249 |   |   | <b>600 mg n=158</b>    | <b>600 mg n=223</b>    |
| 250 |   | <b>400 mg</b>                           | <b>400 mg n=77</b>     | <b>400 mg n=37</b>     |
| 251 |   | <b>% of patients [CI<sub>95%</sub>]</b> |                        |                        |
| 252 | <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> |
| 253 | Complete Hematologic                              |   |                        |                        |
| 254 | Response (CHR)                                    | 95%                                     | 38%                    | 7%                     |
| 255 | No Evidence of Leukemia (NEL)                     | Not applicable                          | 13%                    | 5%                     |
| 256 | Return to Chronic                                 |   |                        |                        |
| 257 | Phase (RTC)                                       | Not applicable                          | 20%                    | 18%                    |
| 258 | <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>   |
| 259 | (Unconfirmed <sup>3</sup> )                       | (65%)                                   | (27%)                  | (15%)                  |
| 260 | Complete <sup>4</sup> (Unconfirmed <sup>3</sup> ) | 39% (47%)                               | 16% (20%)              | 2% (7%)                |

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

262 CHR: Chronic phase study [WBC <10 x 10<sup>9</sup>/L, platelet <450 x 10<sup>9</sup>/L, myelocytes + metamyelocytes  
263 <5% in blood, no blasts and promyelocytes in blood, basophils <20%, no extramedullary  
264 involvement] and in the accelerated and blast crisis studies [ANC ≥1.5 x 10<sup>9</sup>/L, platelets ≥100 x  
265 10<sup>9</sup>/L, no blood blasts, BM blasts <5% and no extramedullary disease]

266 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  
267 crisis studies)

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

270 BM=bone marrow, PB=peripheral blood

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

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

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

278            The median time to hematologic response was 1 month. In late chronic phase CML,  
279 with a median time from diagnosis of 32 months, an estimated 87.8% of patients who  
280 achieved MCyR maintain their response 2 years after achieving their initial response. After 2  
281 years of treatment, an estimated 85.4% of patients were free of progression to AP or BC , and  
282 estimated overall survival was 90.8% [88.3, 93.2]. In accelerated phase, median duration of  
283 hematologic response was 28.8 months for patients with an initial dose of 600 mg (16.5  
284 months for 400 mg, p=0.0035). An estimated 63.8% of patients who achieved MCyR were  
285 still in response 2 years after achieving initial response. The median survival was 20.9 [13.1,  
286 34.4] months for the 400 mg group and was not yet reached for the 600 mg group (p=0.0097).  
287 An estimated 46.2% [34.7, 57.7] vs. 65.8% [58.4, 73.3] of patients were still alive after 2  
288 years of treatment in the 400-mg vs. 600-mg dose groups, respectively (p=0.0088). In blast  
289 crisis, the estimated median duration of hematologic response is 10 months. An estimated  
290 27.2% [16.8, 37.7] of hematologic responders maintained their response 2 years after  
291 achieving their initial response. Median survival was 6.9 [5.8, 8.6] months, and an estimated  
292 18.3% [13.4, 23.3] of all patients with blast crisis were alive 2 years after start of study.



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

## 296 **Pediatric CML**

297 One open-label, single-arm study enrolled 14 pediatric patients with Ph+ chronic phase CML  
298 recurrent after stem cell transplant or resistant to alpha interferon therapy. Patients ranged in  
299 age from 3 to 20 years old; 3 were 3-11 years old, 9 were 12-18 years old, and 2 were >18  
300 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),  
301 440 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  
302 are available, 4 achieved a major cytogenetic response, 7 achieved a complete cytogenetic  
303 response, and 2 had minimal cytogenetic response. At the recommended dose of  
304 260 mg/m<sup>2</sup>/day, 2 of 3 patients achieved a complete cytogenetic response. Cytogenetic  
305 response rate was similar at all dose levels.

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

## 308 **Gastrointestinal Stromal Tumors**

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

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

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

| 322 | <b>Total Patients</b> | <b>N</b> | <b>Confirmed Partial Response N (%)</b> | <b>95% Confidence Interval</b> |
|-----|-----------------------|----------|---|--------------------------------|
| 323 | 400 mg daily          | 73       | 24 (33%)                                | 22%, 45%                       |
| 324 | 600 mg daily          | 74       | 32 (43%)                                | 32%, 55%                       |
| 325 | Total                 | 147      | 56 (38%)                                | 30%, 46%                       |

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

## 332 **INDICATIONS AND USAGE**

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

336 Gleevec is also indicated for the treatment of patients with Philadelphia chromosome  
337 positive chronic myeloid leukemia (CML) in blast crisis, accelerated phase, or in chronic  
338 phase after failure of interferon-alpha therapy. Gleevec is also indicated for the treatment of  
339 pediatric patients with Ph+ chronic phase CML whose disease has recurred after stem cell  
340 transplant or who are resistant to interferon-alpha therapy. There are no controlled trials in  
341 pediatric patients demonstrating a clinical benefit, such as improvement in disease-related  
342 symptoms or increased survival.

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

## 349 **CONTRAINDICATIONS**

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

## 352 **WARNINGS**

### 353 **Pregnancy**

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

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

364 Male and female rats were exposed *in utero* to a maternal imatinib mesylate dose of  
365 45 mg/kg (approximately one-half the maximum human dose of 800 mg) from day 6 of  
366 gestation and through milk during the lactation period. These animals then received no  
367 imatinib exposure for nearly 2 months. Body weights were reduced from birth until terminal  
368 sacrifice in these rats. Although fertility was not affected, fetal loss was seen when these male  
369 and female animals were then mated.

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

## 373   **PRECAUTIONS**

### 374   **General**

375

376   ***Dermatologic Toxicities:*** Bullous dermatologic reactions, including erythema multiforme  
377 and Stevens Johnson syndrome, have been reported with use of Gleevec® (imatinib mesylate).  
378 In some cases reported during post- marketing surveillance, a recurrent dermatologic reaction  
379 was observed upon rechallenge. Several foreign post-marketing reports have described cases  
380 in which patients tolerated the reintroduction of Gleevec therapy after resolution or  
381 improvement of the bullous reaction. In these instances, Gleevec was resumed at a dose lower  
382 than that at which the reaction occurred and some patients also received concomitant  
383 treatment with corticosteroids or antihistamines.

384

385   ***Fluid Retention and Edema:*** Gleevec is often associated with edema and occasionally  
386 serious fluid retention (see ADVERSE REACTIONS). Patients should be weighed and  
387 monitored regularly for signs and symptoms of fluid retention. An unexpected rapid weight  
388 gain should be carefully investigated and appropriate treatment provided. The probability of  
389 edema was increased with higher Gleevec dose and age >65 years in the CML studies. Severe  
390 superficial edema was reported in 1.1% of newly diagnosed CML patients taking Gleevec,  
391 and in 2%-6% of other adult CML patients taking Gleevec. In addition, other severe fluid  
392 retention (e.g., pleural effusion, pericardial effusion, pulmonary edema, and ascites) events  
393 were reported in 0.7% of newly diagnosed CML patients taking Gleevec, and in 2%-6% of  
394 other adult CML patients taking Gleevec. There have been post-marketing reports, including  
395 fatalities, of cerebral edema, increased intracranial pressure, and papilledema in patients with  
396 CML treated with Gleevec.

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

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

401   ***Hemorrhage:*** In the newly diagnosed CML trial, 1.1% of patients had grade 3/4 hemorrhage.  
402 In the GIST clinical trial seven patients (5%), four in the 600-mg dose group and three in the  
403 400-mg dose group, had a total of eight events of CTC grade 3/4 - gastrointestinal (GI) bleeds  
404 (3 patients), intra-tumoral bleeds (3 patients) or both (1 patient). Gastrointestinal tumor sites  
405 may have been the source of GI bleeds.

406   ***Hematologic Toxicity:*** Treatment with Gleevec is associated with anemia, neutropenia, and  
407 thrombocytopenia. Complete blood counts should be performed weekly for the first month,  
408 biweekly for the second month, and periodically thereafter as clinically indicated (for example  
409 every 2-3 months). In CML, the occurrence of these cytopenias is dependent on the stage of

410 disease and is more frequent in patients with accelerated phase CML or blast crisis than in  
411 patients with chronic phase CML. (See DOSAGE AND ADMINISTRATION.)

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

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

## 430 Drug Interactions

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

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

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

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

439 Substances that are inducers of CYP3A4 activity may increase metabolism and decrease  
440 imatinib plasma concentrations. Co-medications that induce CYP3A4 (e.g., dexamethasone,  
441 phenytoin, carbamazepine, rifampin, phenobarbital or St. John's Wort) may significantly  
442 reduce exposure to Gleevec. Pretreatment of healthy volunteers with multiple doses of  
443 rifampin followed by a single dose of Gleevec, increased Gleevec oral-dose clearance by  
444 3.8-fold, which significantly ( $p < 0.05$ ) decreased mean  $C_{max}$  and  $AUC_{(0-\infty)}$ . In patients where  
445 rifampin or other CYP3A4 inducers are indicated, alternative therapeutic agents with less  
446 enzyme induction potential should be considered. (See CLINICAL PHARMACOLOGY and  
447 DOSAGE AND ADMINISTRATION.)

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

449 Gleevec increases the mean  $C_{max}$  and AUC of simvastatin (CYP3A4 substrate) 2- and  
450 3.5-fold, respectively, suggesting an inhibition of the CYP3A4 by Gleevec. Particular caution  
451 is recommended when administering Gleevec with CYP3A4 substrates that have a narrow  
452 therapeutic window (e.g., cyclosporine or pimozide). Gleevec will increase plasma  
453 concentration of other CYP3A4 metabolized drugs (e.g., triazolo-benzodiazepines,  
454 dihydropyridine calcium channel blockers, certain HMG-CoA reductase inhibitors, etc.).

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

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

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

462 Carcinogenicity studies have not been performed with imatinib mesylate.

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

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

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

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

#### 482 **Nursing Mothers**

483 It is not known whether imatinib mesylate or its metabolites are excreted in human milk.  
484 However, in lactating female rats administered 100 mg/kg, a dose approximately equal to the  
485 maximum clinical dose of 800 mg/day based on body surface area, imatinib and its  
486 metabolites were extensively excreted in milk. Concentration in milk was approximately

487 three-fold higher than in plasma. It is estimated that approximately 1.5% of a maternal dose is  
488 excreted into milk, which is equivalent to a dose to the infant of 30% the maternal dose per  
489 unit body weight. Because many drugs are excreted in human milk and because of the  
490 potential for serious adverse reactions in nursing infants, women should be advised against  
491 breast-feeding while taking Gleevec.

## 492 **Pediatric Use**

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

## 496 **Geriatric Use**

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

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

## 507 **ADVERSE REACTIONS**

### 508 **Chronic Myeloid Leukemia**

509 The majority of Gleevec-treated patients experienced adverse events at some time. Most  
510 events were of mild-to-moderate grade, but drug was discontinued for drug-related adverse  
511 events in 3.1% of newly diagnosed patients, 4% of patients in chronic phase after failure of  
512 interferon therapy, 4% in accelerated phase and 5% in blast crisis.

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

519 A variety of adverse events represent local or general fluid retention including pleural  
520 effusion, ascites, pulmonary edema and rapid weight gain with or without superficial edema.  
521 These events appear to be dose related, were more common in the blast crisis and accelerated  
522 phase studies (where the dose was 600 mg/day), and are more common in the elderly. These  
523 events were usually managed by interrupting Gleevec treatment and with diuretics or other  
524 appropriate supportive care measures. However, a few of these events may be serious or life

525 threatening, and one patient with blast crisis died with pleural effusion, congestive heart  
526 failure, and renal failure.

527 Adverse events, regardless of relationship to study drug, that were reported in at least  
528 10% of the patients treated in the Gleevec studies are shown in Tables 4 and 5.

529 **Table 4** Adverse Experiences Reported in Newly Diagnosed CML Clinical Trial  
 530 ( $\geq 10\%$  of all patients)<sup>(1)</sup>

| 531 | 532                    | All Grades |           | CTC Grades 3/4 |           |
|-----|------------------------|------------|-----------|----------------|-----------|
|     |                        | Gleevec®   | IFN+Ara-C | Gleevec®       | IFN+Ara-C |
| 533 | Preferred Term         | N=551 (%)  | N=533 (%) | N=551 (%)      | N=533 (%) |
| 534 | Fluid Retention        | 59.2       | 10.7      | 1.8            | 0.9       |
| 535 | - Superficial Edema    | 57.5       | 9.2       | 1.1            | 0.4       |
| 536 | - Other Fluid          |            |           |                |           |
| 537 | Retention Events       | 6.9        | 1.9       | 0.7            | 0.6       |
| 538 | Nausea                 | 47.0       | 61.5      | 0.9            | 5.1       |
| 539 | Muscle Cramps          | 43.2       | 11.4      | 1.6            | 0.2       |
| 540 | Musculoskeletal Pain   | 39.9       | 44.1      | 3.4            | 8.1       |
| 541 | Diarrhea               | 38.5       | 42.0      | 2.0            | 3.2       |
| 542 | Rash and related terms | 37.2       | 25.7      | 2.4            | 2.4       |
| 543 | Fatigue                | 37.0       | 66.8      | 1.6            | 25.0      |
| 544 | Headache               | 33.6       | 43.3      | 0.5            | 3.6       |
| 545 | Joint Pain             | 30.3       | 39.4      | 2.5            | 7.3       |
| 546 | Abdominal Pain         | 29.9       | 25.0      | 2.5            | 3.9       |
| 547 | Nasopharyngitis        | 26.9       | 8.4       | 0              | 0.2       |
| 548 | Hemorrhage             | 24.1       | 20.8      | 1.1            | 1.5       |
| 549 | - GI hemorrhages       | 1.3        | 1.1       | 0.5            | 0.2       |
| 550 | - CNS hemorrhages      | 0.2        | 0.2       | 0              | 0.2       |
| 551 | Myalgia                | 22.5       | 38.8      | 1.5            | 8.1       |
| 552 | Vomiting               | 20.5       | 27.4      | 1.5            | 3.4       |
| 553 | Dyspepsia              | 17.8       | 9.2       | 0              | 0.8       |
| 554 | Cough                  | 17.4       | 23.1      | 0.2            | 0.6       |
| 555 | Pharyngolaryngeal Pain | 16.9       | 11.3      | 0.2            | 0         |
| 556 | Upper Respiratory      |            |           |                |           |
| 557 | Tract Infection        | 16.5       | 8.4       | 0.2            | 0.4       |
| 558 | Dizziness              | 15.8       | 24.2      | 0.9            | 3.6       |
| 559 | Pyrexia                | 15.4       | 42.4      | 0.9            | 3.0       |
| 560 | Weight Increased       | 15.2       | 2.1       | 1.6            | 0.4       |
| 561 | Insomnia               | 13.2       | 18.8      | 0              | 2.3       |
| 562 | Depression             | 12.7       | 35.8      | 0.5            | 13.1      |
| 563 | Influenza              | 11.1       | 6.0       | 0.2            | 0.2       |

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



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

| 568<br>569<br>570<br>571<br>572<br>573<br>574<br>575<br>576<br>577<br>578<br>579<br>580<br>581<br>582<br>583<br>584<br>585<br>586<br>587<br>588<br>589<br>590<br>591<br>592<br>593<br>594<br>595<br>596<br>597<br>598<br>599<br>600<br>601<br>602<br>603<br>604<br>605<br>606<br>607<br>608<br>609<br>610<br>611<br>612<br>613 | Myeloid Blast<br>Crisis<br>(n= 260)<br>% |        | Accelerated<br>Phase<br>(n=235)<br>% |        | Chronic Phase,<br>IFN Failure<br>(n=532)<br>% |        |
|--|--|--------|--------------------------------------|--------|---|--------|
|  | All                                      | Grade  | All                                  | Grade  | All   | Grade  |
|  | Preferred Term                           | Grades | 3/4                                  | Grades | 3/4   | Grades |
| Fluid Retention  | 72                                       | 11     | 76                                   | 6      | 69  | 4      |
| - Superficial Edema  | 66                                       | 6      | 74                                   | 3      | 67  | 2      |
| - Other Fluid Retention Events <sup>(2)</sup>  | 22                                       | 6      | 15                                   | 4      | 7   | 2      |
| Nausea   | 71                                       | 5      | 73                                   | 5      | 63  | 3      |
| Muscle Cramps  | 28                                       | 1      | 47                                   | 0.4    | 62  | 2      |
| Vomiting   | 54                                       | 4      | 58                                   | 3      | 36  | 2      |
| Diarrhea   | 43                                       | 4      | 57                                   | 5      | 48  | 3      |
| Hemorrhage   | 53                                       | 19     | 49                                   | 11     | 30  | 2      |
| - CNS Hemorrhage   | 9  | 7      | 3                                    | 3      | 2   | 1      |
| - Gastrointestinal Hemorrhage  | 8  | 4      | 6                                    | 5      | 2   | 0.4    |
| Musculoskeletal Pain   | 42                                       | 9      | 49                                   | 9      | 38  | 2      |
| Fatigue  | 30                                       | 4      | 46                                   | 4      | 48  | 1      |
| Skin Rash  | 36                                       | 5      | 47                                   | 5      | 47  | 3      |
| Pyrexia  | 41                                       | 7      | 41                                   | 8      | 21  | 2      |
| Arthralgia   | 25                                       | 5      | 34                                   | 6      | 40  | 1      |
| Headache   | 27                                       | 5      | 32                                   | 2      | 36  | 0.6    |
| Abdominal Pain   | 30                                       | 6      | 33                                   | 4      | 32  | 1      |
| Weight Increased   | 5  | 1      | 17                                   | 5      | 32  | 7      |
| Cough  | 14                                       | 0.8    | 27                                   | 0.9    | 20  | 0      |
| Dyspepsia  | 12                                       | 0      | 22                                   | 0      | 27  | 0      |
| Myalgia  | 9  | 0      | 24                                   | 2      | 27  | 0.2    |
| Nasopharyngitis  | 10                                       | 0      | 17                                   | 0      | 22  | 0.2    |
| Asthenia   | 18                                       | 5      | 21                                   | 5      | 15  | 0.2    |
| Dyspnea  | 15                                       | 4      | 21                                   | 7      | 12  | 0.9    |
| Upper Respiratory Tract Infection  | 3  | 0      | 12                                   | 0.4    | 19  | 0      |
| Anorexia   | 14                                       | 2      | 17                                   | 2      | 7   | 0      |
| Night Sweats   | 13                                       | 0.8    | 17                                   | 1      | 14  | 0.2    |
| Constipation   | 16                                       | 2      | 16                                   | 0.9    | 9   | 0.4    |
| Dizziness  | 12                                       | 0.4    | 13                                   | 0      | 16  | 0.2    |
| Pharyngitis  | 10                                       | 0      | 12                                   | 0      | 15  | 0      |
| Insomnia   | 10                                       | 0      | 14                                   | 0      | 14  | 0.2    |
| Pruritus   | 8  | 1      | 14                                   | 0.9    | 14  | 0.8    |
| Hypokalemia  | 13                                       | 4      | 9                                    | 2      | 6   | 0.8    |
| Pneumonia  | 13                                       | 7      | 10                                   | 7      | 4   | 1      |
| Anxiety  | 8  | 0.8    | 12                                   | 0      | 8   | 0.4    |
| Liver Toxicity   | 10                                       | 5      | 12                                   | 6      | 6   | 3      |
| Rigors   | 10                                       | 0      | 12                                   | 0.4    | 10  | 0      |
| Chest Pain   | 7  | 2      | 10                                   | 0.4    | 11  | 0.8    |
| Influenza  | 0.8                                      | 0.4    | 6                                    | 0      | 11  | 0.2    |
| Sinusitis  | 4  | 0.4    | 11                                   | 0.4    | 9   | 0.4    |

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

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

## 618 **Hematologic Toxicity**

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

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

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

## 630 **Hepatotoxicity**

631 Severe elevation of transaminases or bilirubin occurred in 3%-6% (see Table 5) and were  
632 usually managed with dose reduction or interruption (the median duration of these episodes  
633 was approximately one week). Treatment was discontinued permanently because of liver  
634 laboratory abnormalities in less than 1% of patients. However, one patient, who was taking  
635 acetaminophen regularly for fever, died of acute liver failure.

## 636 **Adverse Reactions in Pediatric Population**

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

## 640 **Adverse Effects in Other Subpopulations**

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

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

|                                 | Gleevec®<br>N=551<br>% |         | IFN+Ara-C<br>N=533<br>% |         |
|---------------------------------|------------------------|---------|-------------------------|---------|
| CTC Grades                      | Grade 3                | Grade 4 | Grade 3                 | Grade 4 |
| <b>Hematology Parameters</b>    |                        |         |                         |         |
| - Neutropenia*                  | 12.3                   | 3.1     | 20.8                    | 4.3     |
| - Thrombocytopenia*             | 8.3                    | 0.2     | 15.9                    | 0.6     |
| - Anemia                        | 3.1                    | 0.9     | 4.1                     | 0.2     |
| <b>Biochemistry Parameters</b>  |                        |         |                         |         |
| - Elevated Creatinine           | 0                      | 0       | 0.4                     | 0       |
| - Elevated Bilirubin            | 0.7                    | 0.2     | 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       |

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

663 **Table 7 Lab Abnormalities in Other CML Clinical Trials**

| Myeloid Blast                   | Accelerated       |         | Chronic Phase,   |         | IFN Failure |         |
|---------------------------------|-------------------|---------|------------------|---------|-------------|---------|
|                                 | Crisis<br>(n=260) |         | Phase<br>(n=235) |         | (n=532)     |         |
|                                 | 600 mg n=223      |         | 600 mg n=158     |         | 400 mg      |         |
|                                 | 400 mg n=37       |         | 400 mg n=77      |         | 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       |

683 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  $\geq 10-50 \times 10^9/L$ , grade 4  $< 10 \times 10^9/L$ ), anemia (hemoglobin  $\geq 65-80$  g/L, grade 4  $< 65$  g/L), elevated creatinine (grade 3  $> 3-6$  x upper limit normal range [ULN], grade 4  $> 6$  x ULN), elevated bilirubin (grade 3  $> 3-10$  x ULN, grade 4  $> 10$  x ULN), elevated alkaline phosphatase (grade 3  $> 5-20$  x ULN, grade 4  $> 20$  x ULN), elevated SGOT or SGPT (grade 3  $> 5-20$  x ULN, grade 4  $> 20$  x ULN)

688 **Gastrointestinal Stromal Tumors**

689 The majority of Gleevec-treated patients experienced adverse events at some time. The most  
690 frequently reported adverse events were edema, nausea, diarrhea, abdominal pain, muscle

691 cramps, fatigue, and rash. Most events were of mild-to-moderate severity. Drug was  
692 discontinued for adverse events in 6 patients (8%) in both dose levels studied. Superficial  
693 edema, most frequently periorbital or lower extremity edema, was managed with diuretics,  
694 other supportive measures, or by reducing the dose of Gleevec<sup>®</sup> (imatinib mesylate).  
695 (See DOSAGE AND ADMINISTRATION.) Severe (CTC grade 3/4) superficial edema was  
696 observed in 3 patients (2%), including face edema in one patient. Grade 3/4 pleural effusion  
697 or ascites was observed in 3 patients (2%).

698 Adverse events, regardless of relationship to study drug, that were reported in at least  
699 10% of the patients treated with Gleevec are shown in Table 8. No major differences were  
700 seen in the severity of adverse events between the 400-mg or 600-mg treatment groups,  
701 although overall incidence of diarrhea, muscle cramps, headache, dermatitis, and edema was  
702 somewhat higher in the 600-mg treatment group.

703 **Table 8** Adverse Experiences Reported in GIST Trial ( $\geq 10\%$  of all patients at either  
704 dose)<sup>(1)</sup>

| 705 | 706                               | All CTC Grades        |        | CTC Grade 3/4         |        |
|-----|-----------------------------------|-----------------------|--------|-----------------------|--------|
|     |                                   | Initial dose (mg/day) |        | Initial dose (mg/day) |        |
| 707 | 708                               | 400 mg                | 600 mg | 400 mg                | 600 mg |
| 709 |                                   | (n=73)                | (n=74) | (n=73)                | (n=74) |
|     | Preferred Term                    | %                     | %      | %                     | %      |
| 710 | Fluid Retention                   | 71                    | 76     | 6                     | 3      |
| 711 | - Superficial Edema               | 71                    | 76     | 4                     | 0      |
| 712 | - Pleural Effusion or Ascites     | 6                     | 4      | 1                     | 3      |
| 713 | Diarrhea                          | 56                    | 60     | 1                     | 4      |
| 714 | Nausea                            | 53                    | 56     | 3                     | 3      |
| 715 | Fatigue                           | 33                    | 38     | 1                     | 0      |
| 716 | Muscle Cramps                     | 30                    | 41     | 0                     | 0      |
| 717 | Abdominal Pain                    | 37                    | 37     | 7                     | 3      |
| 718 | Skin Rash                         | 26                    | 38     | 3                     | 3      |
| 719 | Headache                          | 25                    | 35     | 0                     | 0      |
| 720 | Vomiting                          | 22                    | 23     | 1                     | 3      |
| 721 | Musculoskeletal Pain              | 19                    | 11     | 3                     | 0      |
| 722 | Flatulence                        | 16                    | 23     | 0                     | 0      |
| 723 | Any Hemorrhage                    | 18                    | 19     | 5                     | 8      |
| 724 | - Tumor Hemorrhage                | 1                     | 4      | 1                     | 4      |
| 725 | - Cerebral Hemorrhage             | 1                     | 0      | 1                     | 0      |
| 726 | - GI Tract Hemorrhage             | 6                     | 4      | 4                     | 1      |
| 727 | Nasopharyngitis                   | 12                    | 14     | 0                     | 0      |
| 728 | Pyrexia                           | 12                    | 5      | 0                     | 0      |
| 729 | Insomnia                          | 11                    | 11     | 0                     | 0      |
| 730 | Back Pain                         | 11                    | 10     | 1                     | 0      |
| 731 | Lacrimation Increased             | 6                     | 11     | 0                     | 0      |
| 732 | Upper Respiratory Tract Infection | 6                     | 11     | 0                     | 0      |
| 733 | Taste Disturbance                 | 1                     | 14     | 0                     | 0      |

734 <sup>(1)</sup> All adverse events occurring in  $\geq 10\%$  of patients are listed regardless of suspected relationship  
735 to treatment. Clinically relevant or severe abnormalities of routine hematologic or biochemistry  
736 laboratory values are presented in Table 9.

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

| 738 | 739                             | 400 mg  |         | 600 mg  |         |
|-----|---------------------------------|---------|---------|---------|---------|
|     |                                 | (n=73)  |         | (n=74)  |         |
| 740 |                                 | %       |         | %       |         |
| 741 | CTC Grades                      | Grade 3 | Grade 4 | Grade 3 | Grade 4 |
| 742 | <b>Hematology Parameters</b>    |         |         |         |         |
| 743 | - Anemia                        | 3       | 0       | 4       | 1       |
| 744 | - Thrombocytopenia              | 0       | 0       | 1       | 0       |
| 745 | - Neutropenia                   | 3       | 3       | 5       | 4       |
| 746 | <b>Biochemistry Parameters</b>  |         |         |         |         |
| 747 | - Elevated Creatinine           | 0       | 1       | 3       | 0       |
| 748 | - Reduced Albumin               | 3       | 0       | 4       | 0       |
| 749 | - Elevated Bilirubin            | 1       | 0       | 1       | 3       |
| 750 | - Elevated Alkaline Phosphatase | 0       | 0       | 1       | 0       |

|     |   |   |   |   |   |
|-----|---|---|---|---|---|
| 751 | - Elevated SGOT (AST)   | 3 | 0 | 1 | 1 |
| 752 | - Elevated SGPT (ALT)   | 3 | 0 | 4 | 0 |
| 753 | 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 $\geq 10$ - $50 \times 10^9/L$ , grade 4 $< 10 \times 10^9/L$ ), anemia (grade 3 $\geq 65$ - $80$ g/L, grade 4 $< 65$ g/L), elevated creatinine (grade 3 $> 3$ - $6 \times$ upper limit normal range [ULN], grade 4 $> 6 \times$ ULN), elevated bilirubin (grade 3 $> 3$ - $10 \times$ ULN, grade 4 $> 10 \times$ ULN), elevated alkaline phosphatase, SGOT or SGPT (grade 3 $> 5$ - $20 \times$ ULN, grade 4 $> 20 \times$ ULN), albumin (grade 3 $< 20$ g/L) |   |   |   |   |

## 758 Additional Data From Multiple Clinical Trials

759

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

763

764 **Cardiovascular:** *Infrequent:* cardiac failure, tachycardia, hypertension, hypotension, flushing,  
765 peripheral coldness *Rare:* pericarditis

766

767 **Clinical Laboratory Tests:** *Infrequent:* blood CPK increased, blood LDH increased

768

769 **Dermatologic:** *Less common:* dry skin, alopecia *Infrequent:* exfoliative dermatitis, bullous  
770 eruption, nail disorder, skin pigmentation changes, photosensitivity reaction, purpura,  
771 psoriasis *Rare:* vesicular rash, Stevens-Johnson syndrome, acute generalized exanthematous  
772 pustulosis

773

774 **Digestive:** *Less common:* abdominal distension, gastroesophageal reflux, mouth ulceration  
775 *Infrequent:* gastric ulcer, gastroenteritis, gastritis *Rare:* colitis, ileus/intestinal obstruction,  
776 pancreatitis

777

778 **General Disorders and Administration Site Conditions:** *Rare:* tumor necrosis

779

780 **Hematologic:** *Infrequent:* pancytopenia *Rare:* aplastic anemia

781

782 **Hypersensitivity:** *Rare:* angioedema

783

784 **Infections:** *Infrequent:* sepsis, herpes simplex, herpes zoster

785

786 **Metabolic and Nutritional:** *Infrequent:* hypophosphatemia, dehydration, gout, appetite  
787 disturbances, weight decreased *Rare:* hyperkalemia, hyponatremia

788

789 **Musculoskeletal:** *Less common:* joint swelling *Infrequent:* sciatica, joint and muscle stiffness

790

791 **Nervous System/Psychiatric:** *Less common:* paresthesia *Infrequent:* depression, anxiety,  
792 syncope, peripheral neuropathy, somnolence, migraine, memory impairment *Rare:* increased  
793 intracranial pressure, cerebral edema (including fatalities), confusion, convulsions

794

795 **Renal:** *Infrequent:* renal failure, urinary frequency, hematuria

796

797 **Reproductive:** *Infrequent:* breast enlargement, menorrhagia, sexual dysfunction

798

799 **Respiratory:** *Rare:* interstitial pneumonitis, pulmonary fibrosis

800

801 **Special Senses:** *Less common:* conjunctivitis, vision blurred *Infrequent:* conjunctival

802 hemorrhage, dry eye, vertigo, tinnitus *Rare:* macular edema, papilledema, retinal

803 hemorrhage, glaucoma, vitreous hemorrhage

804

805 **Vascular Disorders:** *Rare:* thrombosis/embolism

## 806 OVERDOSAGE

807 Experience with doses greater than 800 mg is limited. Isolated cases of Gleevec<sup>®</sup> overdose  
808 have been reported. In the event of overdosage, the patient should be observed and  
809 appropriate supportive treatment given.

810 A patient with myeloid blast crisis experienced Grade 1 elevations of serum creatinine, Grade  
811 2 ascites and elevated liver transaminase levels, and Grade 3 elevations of bilirubin after  
812 inadvertently taking 1200 mg of Gleevec daily for 6 days. Therapy was temporarily  
813 interrupted and complete reversal of all abnormalities occurred within one week. Treatment  
814 was resumed at a dose of 400 mg daily without recurrence of adverse events [9]. Another  
815 patient developed severe muscle cramps after taking 1,600 mg of Gleevec daily for 6 days.  
816 Complete resolution of muscle cramps occurred following interruption of therapy and  
817 treatment was subsequently resumed [10]. Another patient that was prescribed 400 mg daily,  
818 took 800 mg of Gleevec on day 1 and 1,200 mg on day 2. Therapy was interrupted, no  
819 adverse events occurred and the patient resumed therapy.

820

## 821 DOSAGE AND ADMINISTRATION

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

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

830 The prescribed dose should be administered orally, with a meal and a large glass of  
831 water. Doses of 400 mg or 600 mg should be administered once-daily, whereas a dose of  
832 800 mg should be administered as 400 mg twice a day.

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

836 For patients unable to swallow the film-coated tablets, the tablets may be dispersed in  
 837 a glass of water or apple juice. The required number of tablets should be placed in the  
 838 appropriate volume of beverage (approximately 50 mL for a 100-mg tablet, and 200 mL for a  
 839 400-mg tablet) and stirred with a spoon. The suspension should be administered immediately  
 840 after complete disintegration of the tablet(s).

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

843 In CML, a dose increase from 400 mg to 600 mg in adult patients with chronic phase  
 844 disease, or from 600 mg to 800 mg (given as 400 mg twice daily) in adult patients in  
 845 accelerated phase or blast crisis may be considered in the absence of severe adverse drug  
 846 reaction and severe non-leukemia related neutropenia or thrombocytopenia in the following  
 847 circumstances: disease progression (at any time); failure to achieve a satisfactory  
 848 hematologic response after at least 3 months of treatment; failure to achieve a cytogenetic  
 849 response after 6-12 months of treatment; or loss of a previously achieved hematologic or  
 850 cytogenetic response. In children with chronic phase CML, daily doses can be increased under  
 851 circumstances similar to those leading to an increase in adult chronic phase disease, from  
 852 260 mg/m<sup>2</sup>/day to 340 mg/m<sup>2</sup>/day, as clinically indicated.

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

## 856 **Dose Adjustment for Hepatotoxicity and Other Non-Hematologic Adverse** 857 **Reactions**

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

861 If elevations in bilirubin >3 x institutional upper limit of normal (IULN) or in liver  
 862 transaminases >5 x IULN occur, Gleevec should be withheld until bilirubin levels have  
 863 returned to a <1.5 x IULN and transaminase levels to <2.5 x IULN. In adults, treatment with  
 864 Gleevec may then be continued at a reduced daily dose (i.e., 400 mg to 300 mg or 600 mg to  
 865 400 mg). In children, daily doses can be reduced under the same circumstances from  
 866 260 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.

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

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

870 **Table 10 Dose Adjustments for Neutropenia and Thrombocytopenia**

|   |                                    |                                      |
|---|------------------------------------|--------------------------------------|
| 871 Chronic Phase CML                   | ANC <1.0 x 10 <sup>9</sup> /L      | 1. Stop Gleevec until ANC            |
| 872 (starting dose 400mg <sup>1</sup> ) | and/or                             | ≥1.5 x 10 <sup>9</sup> /L and        |
| 873 or GIST                             | Platelets <50 x 10 <sup>9</sup> /L | platelets ≥75 x 10 <sup>9</sup> /L   |
| 874 (starting dose either               |                                    | 2. Resume treatment with             |
| 875 400 mg or 600 mg)                   |                                    | Gleevec at the original              |
| 876                                     |                                    | starting dose of 400 mg <sup>1</sup> |
| 877                                     |                                    | or 600 mg                            |



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| 883 |  |  |   |
| 884 |  |  |   |
| 885 | Accelerated Phase  | <sup>3</sup> ANC <0.5 x 10 <sup>9</sup> /L |   |
| 886 | CML and Blast Crisis                                       | and/or                                     |   |
| 887 | (starting dose 600 mg)                                     | Platelets <10 x 10 <sup>9</sup> /L         |   |
| 888 |  |  |   |
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| 898 |  |  |   |
| 899 | <sup>1</sup> or 260 mg/m <sup>2</sup> in children          |  |   |
| 900 | <sup>2</sup> or 200 mg/m <sup>2</sup> in children          |  |   |
| 901 | <sup>3</sup> occurring after at least 1 month of treatment |  |   |
|     |  |  | 3. If recurrence of ANC <1.0 x 10 <sup>9</sup> /L and/or platelets <50 x 10 <sup>9</sup> /L, repeat step 1 and resume Gleevec at a reduced dose (300 mg <sup>2</sup> if starting dose was 400 mg <sup>1</sup> , 400 mg if starting dose was 600 mg) |
|     |  |  | 1. Check if cytopenia is related to leukemia (marrow aspirate or biopsy)  |
|     |  |  | 2. If cytopenia is unrelated to leukemia, reduce dose of Gleevec to 400 mg  |
|     |  |  | 3. If cytopenia persist 2 weeks, reduce further to 300 mg   |
|     |  |  | 4. If cytopenia persist 4 weeks and is still unrelated to leukemia, stop Gleevec until ANC ≥1 x 10 <sup>9</sup> /L and platelets ≥20 x 10 <sup>9</sup> /L and then resume treatment at 300 mg.  |

## 902 HOW SUPPLIED

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

### 904 100 mg Tablets

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

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

### 908 400 mg Tablets

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

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

## 912 Storage

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

915 Dispense in a tight container, USP.

916

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