

4 **Gleevec[®]**

5 **(imatinib mesylate)**

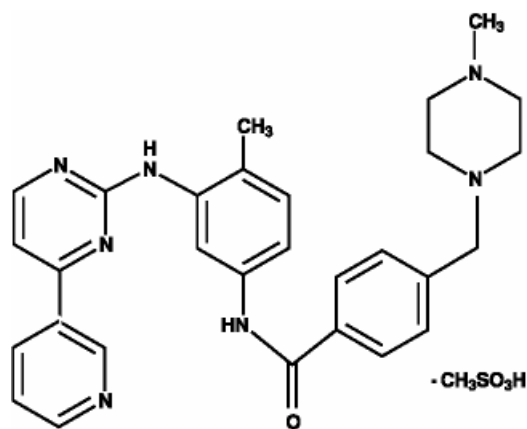
6 **Tablets**

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 as
35 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[®] (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_{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-1,000 mg. There is no significant
48 change in the pharmacokinetics of imatinib on repeated dosing, and accumulation is 1.5-
49 2.5-fold at steady state when Gleevec is dosed once daily. At clinically relevant
50 concentrations of imatinib, binding to plasma proteins in *in vitro* experiments is
51 approximately 95%, mostly to albumin and α_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. The plasma protein binding of the N-demethylated metabolite CGP71588 is similar
60 to that of the parent compound.

61 Elimination is predominately in the feces, mostly as metabolites. Based on the
62 recovery of compound(s) after an oral ¹⁴C-labeled dose of imatinib, approximately 81% of the
63 dose was eliminated within 7 days, in feces (68% of dose) and urine (13% of dose).

64 Unchanged imatinib accounted for 25% of the dose (5% urine, 20% feces), the remainder
65 being metabolites.

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

71 **Special Populations**

72 ***Pediatric:*** As in adult patients, imatinib was rapidly absorbed after oral administration in
73 pediatric patients, with a C_{max} of 2-4 hours. Apparent oral clearance was similar to adult
74 values (11.0 L/hr/m² in children vs. 10.0 L/hr/m² in adults), as was the half-life (14.8 hours in
75 children vs. 17.1 hours in adults). Dosing in children at both 260 mg/m² and 340 mg/m²
76 achieved an AUC similar to the 400-mg dose in adults. The comparison of AUC₍₀₋₂₄₎ on Day 8
77 vs. Day 1 at 260 mg/m² and 340 mg/m² dose levels revealed a 1.5- and 2.2-fold drug
78 accumulation, respectively, after repeated once-daily dosing. Mean imatinib AUC did not
79 increase proportionally with increasing dose.

80 ***Hepatic Insufficiency:*** The effect of hepatic impairment on the pharmacokinetics of both imatinib
81 and its major metabolite, CGP74588, was assessed in 84 cancer patients with varying degrees of
82 hepatic impairment (Table 1) at imatinib doses ranging from 100-800 mg. Exposure to both imatinib
83 and CGP74588 was comparable between each of the mildly and moderately hepatically-impaired
84 groups and the normal group. However, patients with severe hepatic impairment tend to have higher
85 exposure to both imatinib and its metabolite than patients with normal hepatic function. At steady
86 state, the mean $C_{max}/dose$ and AUC₂₄/dose for imatinib increased by about 63% and 45%,
87 respectively, in patients with severe hepatic impairment compared to patients with normal hepatic
88 function. The mean $C_{max}/dose$ and AUC₂₄/dose for CGP74588 increased by about 56% and 55%,
89 respectively, in patients with severe hepatic impairment compared to patients with normal hepatic
90 function. (See PRECAUTIONS and DOSAGE AND ADMINISTRATION).

91

92

Table 1: Liver Function Classification

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

93 ULN=upper limit of normal for the institution

94

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

99 **Drug-Drug Interactions**

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

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

107 **CYP3A4 Inducers:** Pretreatment of 14 healthy volunteers with multiple doses of rifampin,
 108 600 mg daily for 8 days, followed by a single 400-mg dose of Gleevec, increased Gleevec
 109 oral-dose clearance by 3.8-fold (90% confidence interval = 3.5- to 4.3-fold), which represents
 110 mean decreases in C_{max} , $AUC_{(0-24)}$ and $AUC_{(0-\infty)}$ by 54%, 68% and 74%, of the respective
 111 values without rifampin treatment. (See PRECAUTIONS and DOSAGE AND
 112 ADMINISTRATION.)

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

117 CLINICAL STUDIES

118 Chronic Myeloid Leukemia

119 **Chronic Phase, Newly Diagnosed:** An open-label, multicenter, international randomized
120 Phase 3 study has been conducted in patients with newly diagnosed Philadelphia chromosome
121 positive (Ph+) chronic myeloid leukemia (CML) in chronic phase. This study compared
122 treatment with either single-agent Gleevec[®] (imatinib mesylate) or a combination of
123 interferon-alfa (IFN) plus cytarabine (Ara-C). Patients were allowed to cross over to the
124 alternative treatment arm if they failed to show a complete hematologic response (CHR) at 6
125 months, a major cytogenetic response (MCyR) at 12 months, or if they lost a CHR or MCyR.
126 Patients with increasing WBC or severe intolerance to treatment were also allowed to cross
127 over to the alternative treatment arm with the permission of the study monitoring committee
128 (SMC). In the Gleevec arm, patients were treated initially with 400 mg daily. Dose
129 escalations were allowed from 400 mg daily to 600 mg daily, then from 600 mg daily to 800
130 mg daily. In the IFN arm, patients were treated with a target dose of IFN of 5 MIU/m²/day
131 subcutaneously in combination with subcutaneous Ara-C 20 mg/m²/day for 10 days/month.

132 A total of 1,106 patients were randomized from 177 centers in 16 countries, 553 to
133 each arm. Baseline characteristics were well balanced between the two arms. Median age was
134 51 years (range 18-70 years), with 21.9% of patients ≥60 years of age. There were 59% males
135 and 41% females; 89.9% Caucasian and 4.7% Black patients. With a median follow-up of 31
136 and 30 months for Gleevec and IFN, respectively, 79% of patients randomized to Gleevec
137 were still receiving first-line treatment. Due to discontinuations and cross-overs, only 7% of
138 patients randomized to IFN were still on first-line treatment. In the IFN arm, withdrawal of
139 consent (13.6%) was the most frequent reason for discontinuation of first-line therapy, and the
140 most frequent reason for cross over to the Gleevec arm was severe intolerance to treatment
141 (25.1%).

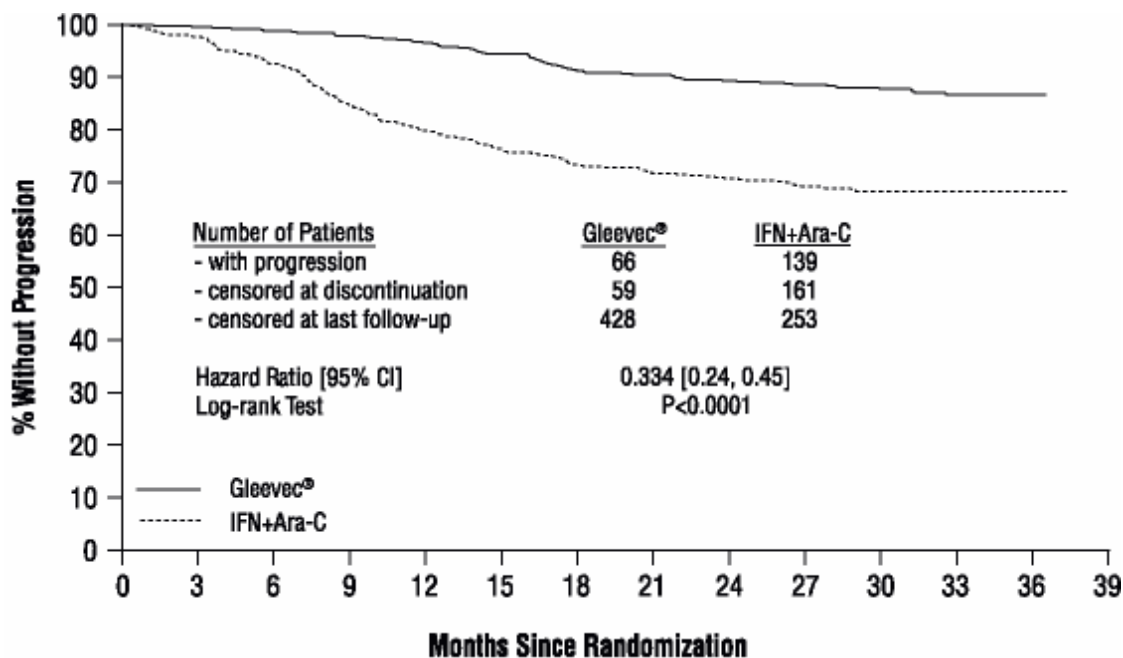
142 The primary efficacy endpoint of the study was progression-free survival (PFS).
143 Progression was defined as any of the following events: progression to accelerated phase or
144 blast crisis, death, loss of CHR or MCyR, or in patients not achieving a CHR an increasing
145 WBC despite appropriate therapeutic management. The protocol specified that the
146 progression analysis would compare the intent to treat (ITT) population: patients randomized
147 to receive Gleevec were compared with patients randomized to receive interferon. Patients
148 that crossed over prior to progression were not censored at the time of cross-over, and events
149 that occurred in these patients following cross-over were attributed to the original randomized
150 treatment. The estimated rate of progression-free survival at 30 months in the ITT population
151 was 87.8% in the Gleevec arm and 68.3% in the IFN arm (p<0.0001), (Figure 1). The
152 estimated rate of patients free of progression to accelerated phase (AP) or blast crisis (BC) at
153 30 months was 94.8% in the Gleevec arm compared to the 89.6%, (p=0.0016) in the IFN arm,
154 (Figure 2). There were 33 and 46 deaths reported in the Gleevec and IFN arm, respectively,
155 with an estimated 30-month survival rate of 94.6% and 91.6%, respectively (differences not
156 significant). The probability of remaining progression-free at 30 months was 100% for
157 patients who were in complete cytogenetic response with major molecular response (≥3-log
158 reduction in Bcr-Abl transcripts as measured by quantitative reverse transcriptase polymerase
159 chain reaction) at 12 months, compared to 93% for patients in complete cytogenetic response

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

162

163

Figure 1 Time to Progression (ITT)

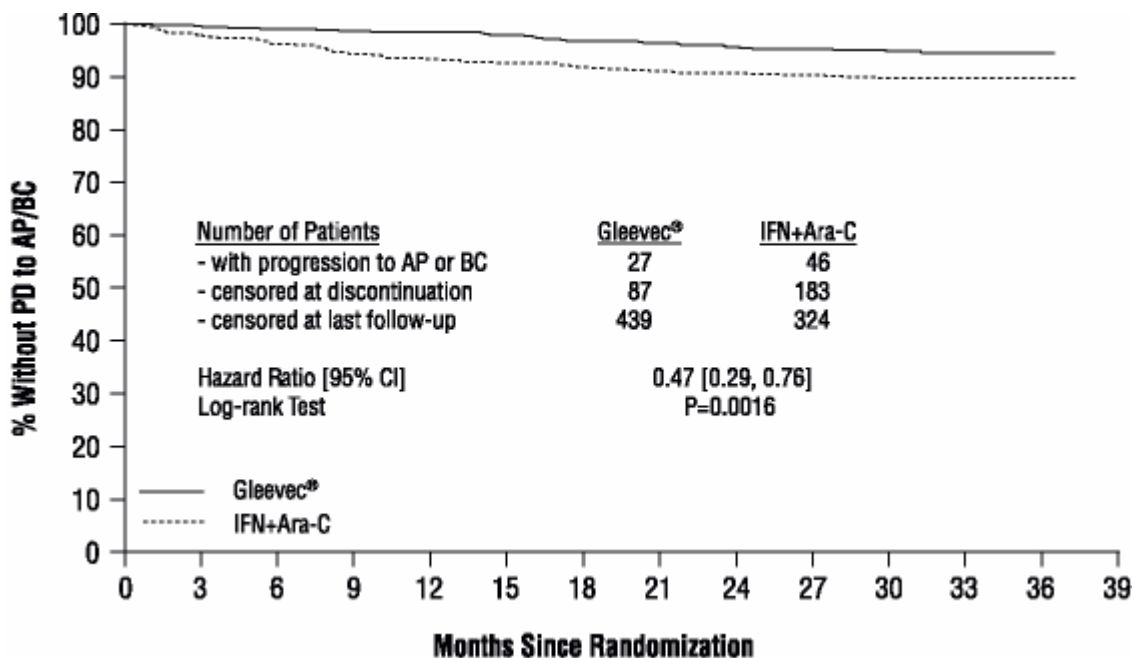


164

165

166

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



167

168 Major cytogenetic response, hematologic response, evaluation of minimal residual
 169 disease (molecular response), time to accelerated phase or blast crisis and survival were main
 170 secondary endpoints. Response data are shown in Table 2. Complete hematologic response,
 171 major cytogenetic response and complete cytogenetic response were also statistically
 172 significantly higher in the Gleevec arm compared to the IFN + Ara-C arm.

173 **Table 2 Response in Newly Diagnosed CML Study (30-Month Data)**

(Best Response Rate)	Gleevec® n=553	IFN+Ara-C n=553
Hematologic Response¹		
CHR Rate n (%)	527 (95.3%)*	308 (55.7%)*
[95% CI]	[93.2%, 96.9%]	[51.4%, 59.9%]
Cytogenetic Response²		
Major Cytogenetic Response n (%)	461 (83.4%)*	90 (16.3%)*
[95% CI]	[80.0%, 86.4%]	[13.3%, 19.6%]
Unconfirmed ³	87.2%*	23.0%*
Complete Cytogenetic Response n (%)	378 (68.4%)*	30 (5.4%)*
Unconfirmed ³	78.8%*	10.7%*
Molecular Response⁴		
Major Response at 12 Months (%)	40%*	2%*
Major Response at 24 Months (%)	54%*	NA ⁵
* p<0.001, Fischer's exact test		
¹ Hematologic response criteria (all responses to be confirmed after ≥4 weeks):		
WBC<10 x 10 ⁹ /L, platelet <450 x 10 ⁹ /L, myelocyte + metamyelocyte <5% in blood, no blasts and promyelocytes in blood, basophils <20%, no extramedullary involvement.		
² Cytogenetic response criteria (confirmed after ≥4 weeks): complete (0% Ph+ metaphases) or partial (1%-35%). A major response (0%-35%) combines both complete and partial responses.		
³ 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.		
⁴ Major molecular response criteria: 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.		
⁵ Not Applicable: insufficient data, only two patients available with samples		

174
 175
 176
 177
 178
 179
 180
 181
 182
 183
 184
 185
 186
 187

188 Physical, functional, and treatment-specific biologic response modifier scales from the
 189 FACT-BRM (Functional Assessment of Cancer Therapy - Biologic Response Modifier)
 190 instrument were used to assess patient-reported general effects of interferon toxicity in 1,067
 191 patients with CML in chronic phase. After one month of therapy to six months of therapy,
 192 there was a 13%-21% decrease in median index from baseline in patients treated with
 193 interferon, consistent with increased symptoms of interferon toxicity. There was no apparent
 194 change from baseline in median index for patients treated with Gleevec.

195 **Late Chronic Phase CML and Advanced Stage CML:** Three international, open-label,
 196 single-arm Phase 2 studies were conducted to determine the safety and efficacy of Gleevec in

197 patients with Ph+ CML: 1) in the chronic phase after failure of IFN therapy, 2) in accelerated
198 phase disease, or 3) in myeloid blast crisis. About 45% of patients were women and 6% were
199 Black. In clinical studies 38%-40% of patients were ≥ 60 years of age and 10%-12% of
200 patients were ≥ 70 years of age.

201 **Chronic Phase, Prior Interferon-Alpha Treatment:** 532 patients were treated at a starting
202 dose of 400 mg; dose escalation to 600 mg was allowed. The patients were distributed in three
203 main categories according to their response to prior interferon: failure to achieve (within 6
204 months), or loss of a complete hematologic response (29%), failure to achieve (within 1 year)
205 or loss of a major cytogenetic response (35%), or intolerance to interferon (36%). Patients had
206 received a median of 14 months of prior IFN therapy at doses $\geq 25 \times 10^6$ IU/week and were all
207 in late chronic phase, with a median time from diagnosis of 32 months. Effectiveness was
208 evaluated on the basis of the rate of hematologic response and by bone marrow exams to
209 assess the rate of major cytogenetic response (up to 35% Ph+ metaphases) or complete
210 cytogenetic response (0% Ph+ metaphases). Median duration of treatment was 29 months
211 with 81% of patients treated for ≥ 24 months (maximum = 31.5 months). Efficacy results are
212 reported in Table 3. Confirmed major cytogenetic response rates were higher in patients with
213 IFN intolerance (66%) and cytogenetic failure (64%), than in patients with hematologic
214 failure (47%). Hematologic response was achieved in 98% of patients with cytogenetic
215 failure, 94% of patients with hematologic failure, and 92% of IFN-intolerant patients.

216 **Accelerated Phase:** 235 patients with accelerated phase disease were enrolled. These patients
217 met one or more of the following criteria: $\geq 15\%$ - $<30\%$ blasts in PB or BM; $\geq 30\%$ blasts +
218 promyelocytes in PB or BM; $\geq 20\%$ basophils in PB; and $<100 \times 10^9/L$ platelets. The first 77
219 patients were started at 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 ≥ 24
225 months (maximum=35 months). Efficacy results are reported in Table 3. 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:** 260 patients with myeloid blast crisis were enrolled. These patients had
230 $\geq 30\%$ blasts in PB or BM and/or extramedullary involvement other than spleen or liver; 95
231 (37%) had received prior chemotherapy for treatment of either accelerated phase or blast
232 crisis ("pretreated patients") whereas 165 (63%) had not ("untreated patients"). The first 37
233 patients were started at 400 mg; the remaining 223 patients were started at 600 mg.

234 Effectiveness was evaluated primarily on the basis of rate of hematologic response,
235 reported as either complete hematologic response, no evidence of leukemia, or return to
236 chronic phase CML using the same criteria as for the study in accelerated phase. Cytogenetic
237 responses were also assessed. Median duration of treatment was 4 months with 21% of
238 patients treated for ≥ 12 months and 10% for ≥ 24 months (maximum=35 months). Efficacy
239 results are reported in Table 3. The hematologic response rate was higher in untreated patients

240 than in treated patients (36% vs. 22%, respectively) and in the group receiving an initial dose
 241 of 600 mg rather than 400 mg (33% vs. 16%). The confirmed and unconfirmed major
 242 cytogenetic response rate was also higher for the 600-mg dose group than for the 400-mg dose
 243 group (17% vs. 8%).

244

Table 3 Response in CML Studies

	Chronic Phase IFN Failure (n=532) 400 mg	Accelerated Phase (n=235) 600 mg n=158 400 mg n=77	Myeloid Blast Crisis (n=260) 600 mg n=223 400 mg n=37
	% of patients [CI_{95%}]		
Hematologic Response¹	95% [92.3–96.3]	71% [64.8–76.8]	31% [25.2–36.8]
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%
Major Cytogenetic Response²	60% [55.3–63.8]	21% [16.2–27.1]	7% [4.5–11.2]
(Unconfirmed ³)	(65%)	(27%)	(15%)
Complete ⁴ (Unconfirmed ³)	39% (47%)	16% (20%)	2% (7%)

245

¹ Hematologic response criteria (all responses to be confirmed after ≥4 weeks):

246

CHR: Chronic phase study [WBC <10 x 10⁹/L, platelet <450 x 10⁹/L, myelocytes + metamyelocytes <5% in blood, no blasts and promyelocytes in blood, basophils <20%, no extramedullary involvement] and in the accelerated and blast crisis studies [ANC ≥1.5 x 10⁹/L, platelets ≥100 x 10⁹/L, no blood blasts, BM blasts <5% and no extramedullary disease]

247

248

249

250

251

NEL: Same criteria as for CHR but ANC ≥1 x 10⁹/L and platelets ≥20 x 10⁹/L (accelerated and blast crisis studies)

252

253

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

254

BM=bone marrow, PB=peripheral blood

255

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

256

257

258

³ 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.

259

260

261

⁴ Complete cytogenetic response confirmed by a second bone marrow cytogenetic evaluation performed at least 1 month after the initial bone marrow study.

262

263

264

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

265

266

267

268

269 of hematologic response was 28.8 months for patients with an initial dose of 600 mg (16.5
270 months for 400 mg, $p=0.0035$). An estimated 63.8% of patients who achieved MCyR were
271 still in response 2 years after achieving initial response. The median survival was 20.9 [13.1,
272 34.4] months for the 400-mg group and was not yet reached for the 600-mg group ($p=0.0097$).
273 An estimated 46.2% [34.7, 57.7] vs. 65.8% [58.4, 73.3] of patients were still alive after 2
274 years of treatment in the 400-mg vs. 600-mg dose groups, respectively ($p=0.0088$). In blast
275 crisis, the estimated median duration of hematologic response is 10 months. An estimated
276 27.2% [16.8, 37.7] of hematologic responders maintained their response 2 years after
277 achieving their initial response. Median survival was 6.9 [5.8, 8.6] months, and an estimated
278 18.3% [13.4, 23.3] of all patients with blast crisis were alive 2 years after start of study.

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

282 **Pediatric CML:** A total of 51 pediatric patients with newly diagnosed and untreated CML in
283 chronic phase were enrolled in an open-label, multicenter, single arm phase 2 trial. Patients
284 were treated with Gleevec 340 mg/m²/day, with no interruptions in the absence of dose
285 limiting toxicity. Complete hematologic response (CHR) was observed in 78% of patients
286 after 8 weeks of therapy. The complete cytogenetic response rate (CCyR) was 65%,
287 comparable to the results observed in adults. Additionally, partial cytogenetic response
288 (PCyR) was observed in 16%. The majority of patients who achieved a CCyR developed the
289 CCyR between months 3 and 10 with a median time to response based on the Kaplan-Meier
290 estimate of 6.74 months.

291 One open-label, single-arm study enrolled 14 pediatric patients with Ph⁺ chronic phase CML
292 recurrent after stem cell transplant or resistant to interferon-alpha therapy. Patients ranged in
293 age from 3-20 years old; 3 were 3-11 years old, 9 were 12-18 years old, and 2 were >18 years
294 old. Patients were treated at doses of 260 mg/m²/day (n=3), 340 mg/m²/day (n=4),
295 440 mg/m²/day (n=5) and 570 mg/m²/day (n=2). In the 13 patients for whom cytogenetic data
296 are available, 4 achieved a partial cytogenetic response, 7 achieved a complete cytogenetic
297 response, and 2 had a minimal cytogenetic response.

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

300 **Gastrointestinal Stromal Tumors**

301 One open-label, multinational study was conducted in patients with unresectable or metastatic
302 malignant gastrointestinal stromal tumors (GIST). In this study, 147 patients were enrolled
303 and randomized to receive either 400 mg or 600 mg orally q.d. for up to 36 months. The study
304 was not powered to show a statistically significant difference in response rates between the 2
305 dose groups. Patients ranged in age from 18 to 83 years old and had a pathologic diagnosis of
306 Kit (CD117) positive unresectable and/or metastatic malignant GIST. Immunohistochemistry
307 was routinely performed with Kit antibody (A-4502, rabbit polyclonal antiserum, 1:100;
308 DAKO Corporation, Carpinteria, CA) according to analysis by an avidin-biotin-peroxidase
309 complex method after antigen retrieval.

310 The primary outcome of the study was objective response rate. Tumors were required
 311 to be measurable at entry in at least one site of disease, and response characterization was
 312 based on Southwestern Oncology Group (SWOG) criteria. Results are shown in Table 4.

313 **Table 4 Tumor Response in GIST Trial**

	(N=147) 400 mg n= 73 600 mg n=74 n (%)
Complete Response	1(0.7)
Partial Response	98 (66.7%)
Total (CR + PR)	99 (67.3% with 95% C.I. 59.1, 74.8)

314 There were no differences in response rates between the 2 dose groups. For the 99
 315 responders to imatinib observed in the GIST study, the Kaplan-Meier estimate of median
 316 duration of response is 118 weeks (95% CI: 96, not reached) The median time to response
 317 was 12 weeks (range was 3-98 weeks).

318

319 INDICATIONS AND USAGE

320 Gleevec[®] (imatinib mesylate) is indicated for the treatment of newly diagnosed adult and
 321 pediatric patients with Philadelphia chromosome positive chronic myeloid leukemia (CML) in
 322 chronic phase. Follow-up is limited.

323 Gleevec is also indicated for the treatment of patients with Philadelphia chromosome
 324 positive chronic myeloid leukemia (CML) in blast crisis, accelerated phase, or in chronic
 325 phase after failure of interferon-alpha therapy. Gleevec is also indicated for the treatment of
 326 pediatric patients with Ph+ chronic phase CML whose disease has recurred after stem cell
 327 transplant or who are resistant to interferon-alpha therapy.

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

334 CONTRAINDICATIONS

335 Use of Gleevec[®] (imatinib mesylate) is contraindicated in patients with hypersensitivity to
 336 imatinib or to any other component of Gleevec.

337 WARNINGS

338 Pregnancy

339

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

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

350 Male and female rats were exposed *in utero* to a maternal imatinib mesylate dose of
351 45 mg/kg (approximately one-half the maximum human dose of 800 mg) from Day 6 of
352 gestation and through milk during the lactation period. These animals then received no
353 imatinib exposure for nearly 2 months. Body weights were reduced from birth until terminal
354 sacrifice in these rats. Although fertility was not affected, fetal loss was seen when these male
355 and female animals were then mated.

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

359 PRECAUTIONS

360 General

361 **Severe congestive heart failure and left ventricular dysfunction:** Severe congestive heart
362 failure and left ventricular dysfunction have occasionally been reported in patients taking
363 Gleevec. Most of the patients with reported cardiac events have had other co-morbidities and
364 risk factors, including advanced age and previous medical history of cardiac disease. In an
365 international randomized phase 3 study in 1,106 patients with newly diagnosed Ph+CML in
366 chronic phase, severe cardiac failure and left ventricular dysfunction was observed in 0.7% of
367 patients taking Gleevec compared to 0.9% of patients taking IFN+Ara-C. Patients with
368 cardiac disease or risk factors for cardiac failure should be monitored carefully and any
369 patient with signs or symptoms consistent with cardiac failure should be evaluated and
370 treated.

371

372 **Dermatologic Toxicities:** Bullous dermatologic reactions, including erythema multiforme
373 and Stevens-Johnson syndrome, have been reported with use of Gleevec[®] (imatinib mesylate).
374 In some cases reported during post-marketing surveillance, a recurrent dermatologic reaction

375 was observed upon rechallenge. Several foreign post-marketing reports have described cases
376 in which patients tolerated the reintroduction of Gleevec therapy after resolution or
377 improvement of the bullous reaction. In these instances, Gleevec was resumed at a dose lower
378 than that at which the reaction occurred and some patients also received concomitant
379 treatment with corticosteroids or antihistamines.

380 **Fluid Retention and Edema:** Gleevec is often associated with edema and occasionally
381 serious fluid retention (see ADVERSE REACTIONS). Patients should be weighed and
382 monitored regularly for signs and symptoms of fluid retention. An unexpected rapid weight
383 gain should be carefully investigated and appropriate treatment provided. The probability of
384 edema was increased with higher Gleevec dose and age >65 years in the CML studies. Severe
385 superficial edema was reported in 1.1% of newly diagnosed CML patients taking Gleevec,
386 and in 2%-6% of other adult CML patients taking Gleevec. In addition, other severe fluid
387 retention (e.g., pleural effusion, pericardial effusion, pulmonary edema, and ascites) events
388 were reported in 0.7% of newly diagnosed CML patients taking Gleevec, and in 2%-6% of
389 other adult CML patients taking Gleevec. Severe superficial edema and severe fluid retention
390 (pleural effusion, pulmonary edema and ascites) were reported in 1%-6% of patients taking
391 Gleevec for GIST.

392 There have been post-marketing reports, including fatalities, of cardiac tamponade,
393 cerebral edema, increased intracranial pressure, and papilledema in patients treated with
394 Gleevec.

395 **Gastrointestinal Disorders:** Gleevec is sometimes associated with GI irritation. Gleevec
396 should be taken with food and a large glass of water to minimize this problem. There have
397 been rare reports, including fatalities, of gastrointestinal perforation.

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

403 **Hematologic Toxicity:** Treatment with Gleevec is associated with anemia, neutropenia, and
404 thrombocytopenia. Complete blood counts should be performed weekly for the first month,
405 biweekly for the second month, and periodically thereafter as clinically indicated (for
406 example, every 2-3 months). In CML, the occurrence of these cytopenias is dependent on the
407 stage of disease and is more frequent in patients with accelerated phase CML or blast crisis
408 than in patients with chronic phase CML. In pediatric CML patients the most frequent
409 toxicities observed were grade 3 or 4 cytopenias including neutropenia, thrombocytopenia and
410 anemia. These generally occur within the first several months of therapy. (See DOSAGE
411 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).

417 **Hepatic Impairment:** Comparable exposure was noted between each of the mildly and
418 moderately hepatically-impaired patients and patients with normal hepatic function. However,
419 patients with severe hepatic impairment tended to have higher exposure to both imatinib and
420 its metabolite than patients with normal hepatic function (See CLINICAL
421 PHARMACOLOGY and DOSING AND ADMINISTRATION). Patients with severe hepatic
422 impairment should be closely monitored.

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

433 **Drug Interactions**

434 ***Drugs that May Alter Imatinib Plasma Concentrations***

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

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

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

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

451 ***Drugs that May Have their Plasma Concentration Altered by Gleevec***

452 Gleevec increases the mean C_{max} and AUC of simvastatin (CYP3A4 substrate) 2- and
453 3.5-fold, respectively, suggesting an inhibition of the CYP3A4 by Gleevec. Particular caution
454 is recommended when administering Gleevec with CYP3A4 substrates that have a narrow
455 therapeutic window (e.g., cyclosporine or pimozone). Gleevec will increase plasma

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

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

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

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

468 **Carcinogenesis, Mutagenesis, Impairment of Fertility**

469 The urogenital tract from a 2-year carcinogenicity study in rats receiving doses of 15, 30 and
470 60 mg/kg/day of imatinib mesylate showed renal adenomas/carcinomas, urinary bladder
471 papillomas and papillomas/carcinomas of the preputial and clitoral gland. Evaluation of other
472 organs in the rats is ongoing.

473 The papilloma/carcinoma of the preputial/clitoral gland were noted at 30 and
474 60 mg/kg/day (approximately 0.5 to 4 times the human daily exposure at 400 mg/day). The
475 kidney adenoma/carcinoma and the urinary bladder papilloma were noted at 60 mg/kg/day.
476 No tumors in the urogenital tract were observed at 15 mg/kg/day.

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

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

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

493 Pregnancy**494 *Pregnancy Category D. (See WARNINGS.)*****495 Nursing Mothers**

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

505 Pediatric Use

506 Gleevec safety and efficacy have been demonstrated in children with newly diagnosed Ph+
507 chronic phase CML and in children with Ph+ chronic phase CML with recurrence after stem
508 cell transplantation or resistance to interferon-alpha therapy. There are no data in children
509 under 2 years of age. Follow-up in children with newly diagnosed Ph+ chronic phase CML is
510 limited.

511 Geriatric Use

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

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

522 ADVERSE REACTIONS**523 Chronic Myeloid Leukemia**

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

528 The most frequently reported drug-related adverse events were edema, nausea and
 529 vomiting, muscle cramps, musculoskeletal pain, diarrhea and rash (Table 5 for newly
 530 diagnosed CML, Table 6 for other CML patients). Edema was most frequently periorbital or
 531 in lower limbs and was managed with diuretics, other supportive measures, or by reducing the
 532 dose of Gleevec[®] (imatinib mesylate). (See DOSAGE AND ADMINISTRATION.) The
 533 frequency of severe superficial edema was 1.1%-6%.

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

542 Adverse events, regardless of relationship to study drug, that were reported in at least
 543 10% of the patients treated in the Gleevec studies are shown in Tables 5 and 6.

544

545 **Table 5 Adverse Experiences Reported in Newly Diagnosed CML Clinical Trial**
 546 **(≥10% of all patients)⁽¹⁾**

Preferred Term	All Grades		CTC Grades 3/4	
	Gleevec [®] N=551 (%)	IFN+Ara-C N=533 (%)	Gleevec [®] N=551 (%)	IFN+Ara-C N=533 (%)
Fluid Retention	59.2	10.7	1.8	0.9
- Superficial Edema	57.5	9.2	1.1	0.4
- Other Fluid Retention Events	6.9	1.9	0.7	0.6
Nausea	47	61.5	0.9	5.1
Muscle Cramps	43.2	11.4	1.6	0.2
Musculoskeletal Pain	39.2	44.1	3.4	8.1
Diarrhea	38.5	42	2.0	3.2
Rash and Related Terms	37.2	25.7	2.4	2.4
Fatigue	37.0	66.8	1.6	25.0
Headache	33.6	43.3	0.5	3.6
Joint Pain	30.3	39.4	2.5	7.3
Abdominal Pain	29.9	25.0	2.5	3.9
Nasopharyngitis	26.9	8.4	0	0.2
Hemorrhage	24.1	20.8	1.1	1.5
- GI Hemorrhage	1.3	1.1	0.5	0.2
- CNS Hemorrhage	0.2	0.2	0	0.2

Myalgia	22.5	38.8	1.5	8.1
Vomiting	20.5	27.4	1.5	3.4
Dyspepsia	17.8	9.2	0	0.8
Cough	17.4	23.1	0.2	0.6
Pharyngolaryngeal Pain	16.9	11.3	0.2	0
Upper Respiratory Tract Infection	16.5	8.4	0.2	0.4
Dizziness	15.8	24.2	0.9	3.6
Pyrexia	15.4	42.4	0.9	3.0
Weight Increased	15.2	2.1	1.6	0.4
Insomnia	13.2	18.8	0	2.3
Depression	12.7	35.8	0.5	13.1
Influenza	11.1	6.0	0.2	0.2

547 (1) All adverse events occurring in $\geq 10\%$ of patients are listed regardless of suspected relationship
548 to treatment.

549 **Table 6 Adverse Experiences Reported in Other CML Clinical Trials ($\geq 10\%$ of all**
550 **patients in any trial)⁽¹⁾**

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
Fluid Retention	72	11	76	6	69	4
- Superficial Edema	66	6	74	3	67	2
- Other Fluid Retention Events ⁽²⁾	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
- GI 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

551 ⁽¹⁾ All adverse events occurring in $\geq 10\%$ of patients are listed regardless of suspected relationship
552 to treatment.

553 ⁽²⁾ Other fluid retention events include pleural effusion, ascites, pulmonary edema, pericardial
554 effusion, anasarca, edema aggravated, and fluid retention not otherwise specified.

555 Hematologic Toxicity

556 Cytopenias, and particularly neutropenia and thrombocytopenia, were a consistent finding in
557 all studies, with a higher frequency at doses ≥ 750 mg (Phase 1 study). However, the
558 occurrence of cytopenias in CML patients was also dependent on the stage of the disease.

559 In patients with newly diagnosed CML, cytopenias were less frequent than in the other
560 CML patients (see Tables 7 and 8). The frequency of grade 3 or 4 neutropenia and
561 thrombocytopenia was between 2- and 3-fold higher in blast crisis and accelerated phase
562 compared to chronic phase (see Tables 7 and 8). The median duration of the neutropenic and
563 thrombocytopenic episodes varied from 2 to 3 weeks, and from 2 to 4 weeks, respectively.

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

567 **Hepatotoxicity**

568 Severe elevation of transaminases or bilirubin occurred in 3%-6% (see Table 7) and were
569 usually managed with dose reduction or interruption (the median duration of these episodes
570 was approximately 1 week). Treatment was discontinued permanently because of liver
571 laboratory abnormalities in less than 0.5% of CML patients. However, one patient, who was
572 taking acetaminophen regularly for fever, died of acute liver failure. In the GIST trial, grade
573 3 or 4 SGPT (ALT) elevations were observed in 6.8% of patients and grade 3 or 4 SGOT
574 (AST) elevations were observed in 4.8% of patients. Bilirubin elevation was observed in
575 2.7% of patients.

576

577 **Adverse Reactions in Pediatric Population**

578 The overall safety profile of pediatric patients treated with Gleevec in 93 children studied was
579 similar to that found in studies with adult patients, except that musculoskeletal pain was less
580 frequent (20.5%) and peripheral edema was not reported. Nausea and vomiting and myalgias
581 were the most commonly reported individual AEs with an incidence similar to that seen in
582 adult patients. Although most patients experienced AEs at some time during the study, the
583 incidence of Grade 3/4 AEs was low.

584 **Adverse Effects in Other Subpopulations**

585 In older patients (≥ 65 years old), with the exception of edema, where it was more frequent,
586 there was no evidence of an increase in the incidence or severity of adverse events. In women
587 there was an increase in the frequency of neutropenia, as well as Grade 1/2 superficial edema,
588 headache, nausea, rigors, vomiting, rash, and fatigue. No differences were seen related to race
589 but the subsets were too small for proper evaluation.

590 **Table 7 Lab Abnormalities in Newly Diagnosed CML Trial**

CTC Grades	Gleevec® N=551 %		IFN+Ara-C N=533 %	
	Grade 3	Grade 4	Grade 3	Grade 4
Hematology Parameters				
- 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
Biochemistry Parameters				

- 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

591 *p<0.001 (difference in Grade 3 plus 4 abnormalities between the two treatment groups)

592

593

Table 8 Lab Abnormalities in Other CML Clinical Trials

	Myeloid Blast Crisis (n=260)		Accelerated Phase (n=235)		Chronic Phase, IFN Failure (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
Hematology Parameters						
- Neutropenia	16	48	23	36	27	9
- Thrombocytopenia	30	33	31	13	21	<1
- Anemia	42	11	34	7	6	1
Biochemistry Parameters						
- 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

594 CTC Grades: neutropenia (Grade 3 $\geq 0.5-1.0 \times 10^9/L$, Grade 4 $< 0.5 \times 10^9/L$), thrombocytopenia (Grade
595 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
596 creatinine (Grade 3 $> 3-6$ x upper limit normal range [ULN], Grade 4 > 6 x ULN), elevated bilirubin
597 (Grade 3 $> 3-10$ x ULN, Grade 4 > 10 x ULN), elevated alkaline phosphatase (Grade 3 $> 5-20$ x ULN,
598 Grade 4 > 20 x ULN), elevated SGOT or SGPT (Grade 3 $> 5-20$ x ULN, Grade 4 > 20 x ULN)
599

600 **Gastrointestinal Stromal Tumors**

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

603 cramps, fatigue, and rash. Most events were of mild-to-moderate severity. Drug was
 604 discontinued for adverse events in 7 patients (5%) in both dose levels studied. Superficial
 605 edema, most frequently periorbital or lower extremity edema, was managed with diuretics,
 606 other supportive measures, or by reducing the dose of Gleevec[®] (imatinib mesylate).
 607 (See DOSAGE AND ADMINISTRATION.) Severe (CTC Grade 3/4) superficial edema was
 608 observed in 3 patients (2%), including face edema in one patient. Grade 3/4 pleural effusion
 609 or ascites was observed in 3 patients (2%).

610 Adverse events, regardless of relationship to study drug, that were reported in at least
 611 10% of the patients treated with Gleevec are shown in Table 15. No major differences were
 612 seen in the severity of adverse events between the 400-mg or 600-mg treatment groups,
 613 although overall incidence of diarrhea, muscle cramps, headache, dermatitis, and edema was
 614 somewhat higher in the 600-mg treatment group.

615

616 **Table 9 Adverse Experiences Reported in GIST Trial ($\geq 10\%$ of all patients at**
 617 **either dose)⁽¹⁾**

	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	81	80	7	12
- Superficial Edema	81	77	6	5
- Pleural Effusion or Ascites	15	12	3	8
Diarrhea	59	70	3	7
Nausea	63	74	6	4
Fatigue	48	53	1	1
Muscle Cramps	47	58	0	0
Abdominal Pain	40	37	11	4
Rash and Related Terms	38	53	4	3
Vomiting	38	35	3	5
Musculoskeletal Pain	37	30	6	1
Headache	33	39	0	0
Flatulence	30	34	0	0
Any Hemorrhage	26	34	6	11
- Tumor Hemorrhage	1	4	1	4
- Cerebral Hemorrhage	1	0	1	0
- GI Tract Hemorrhage	4	4	4	3

- Other Hemorrhage ⁽²⁾	22	27	0	5
Pyrexia	25	16	3	0
Back Pain	23	26	6	0
Nasopharyngitis	21	27	0	0
Insomnia	19	18	1	0
Lacrimation Increased	16	18	0	0
Dyspepsia	15	15	0	0
Upper Respiratory Tract Infection	14	18	0	0
Liver Toxicity	12	12	6	8
Dizziness	12	11	0	0
Loose Stools	12	10	0	0
Operation	12	8	6	4
Pharyngolaryngeal Pain	12	7	0	0
Joint Pain	11	15	1	0
Constipation	11	10	0	1
Anxiety	11	7	0	0
Taste Disturbance	3	15	0	0
<p>⁽¹⁾ All adverse events occurring in $\geq 10\%$ of patients are listed regardless of suspected relationship to treatment.</p> <p>⁽²⁾ This category includes conjunctival hemorrhage, blood in stool, epistaxis, hematuria, post-procedural hemorrhage, bruising, and contusion.</p>				

618 Clinically relevant or severe abnormalities of routine hematologic or biochemistry
619 laboratory values are presented in Table 16.

620 **Table 10 Laboratory Abnormalities in GIST Trial**

CTC Grades	400 mg (n=73) %		600 mg (n=74) %	
	Grade 3	Grade 4	Grade 3	Grade 4
Hematology Parameters				
- Anemia	3	0	8	1
- Thrombocytopenia	0	0	1	0
- Neutropenia	7	3	8	3
Biochemistry Parameters				
- Elevated Creatinine	0	0	3	0
- Reduced Albumin	3	0	4	0
- Elevated Bilirubin	1	0	1	3
- Elevated Alkaline Phosphatase	0	0	3	0
- Elevated SGOT (AST)	4	0	3	3
- Elevated SGPT (ALT)	6	0	7	1

621 CTC Grades: neutropenia (Grade 3 ≥ 0.5 - $1.0 \times 10^9/L$, Grade 4 $< 0.5 \times 10^9/L$), thrombocytopenia (Grade
622 3 ≥ 10 - $50 \times 10^9/L$, Grade 4 $< 10 \times 10^9/L$), anemia (Grade 3 ≥ 65 - 80 g/L, grade 4 < 65 g/L), elevated
623 creatinine (Grade 3 > 3 - $6 \times$ upper limit normal range [ULN], Grade 4 $> 6 \times$ ULN), elevated bilirubin
624 (Grade 3 > 3 - $10 \times$ ULN, Grade 4 $> 10 \times$ ULN), elevated alkaline phosphatase, SGOT or SGPT (Grade 3
625 > 5 - $20 \times$ ULN, Grade 4 $> 20 \times$ ULN), albumin (Grade 3 < 20 g/L)
626

627 **Additional Data From Multiple Clinical Trials**

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

631 **Cardiovascular: Infrequent:** cardiac failure, tachycardia, hypertension, hypotension, flushing,
632 peripheral coldness

633 **Rare:** pericarditis

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

635 **Dermatologic: Less common:** dry skin, alopecia

636 **Infrequent:** exfoliative dermatitis, bullous eruption, nail disorder, skin pigmentation changes,
637 photosensitivity reaction, purpura, psoriasis

638 **Rare:** vesicular rash, Stevens-Johnson syndrome, acute generalized exanthematous pustulosis,
639 acute febrile neutrophilic dermatosis (Sweet's syndrome)

- 640 **Digestive:** *Less common:* abdominal distention, gastroesophageal reflux, mouth ulceration
641 *Infrequent:* gastric ulcer, gastroenteritis, gastritis
- 642 *Rare:* colitis, ileus/intestinal obstruction, pancreatitis, diverticulitis, tumor hemorrhage/tumor
643 necrosis, gastrointestinal perforation (see PRECAUTIONS)
- 644
- 645 **General Disorders and Administration Site Conditions:** *Rare:* tumor necrosis
- 646 **Hematologic:** *Infrequent:* pancytopenia
- 647 *Rare:* aplastic anemia
- 648 **Hepatobiliary:** *Uncommon:* hepatitis
- 649 *rare:* hepatic failure
- 650
- 651 **Hypersensitivity:** *Rare:* angioedema
- 652 **Infections:** *Infrequent:* sepsis, herpes simplex, herpes zoster
- 653 **Metabolic and Nutritional:** *Infrequent:* hypophosphatemia, dehydration, gout, appetite
654 disturbances, weight decreased
- 655 *Rare:* hyperkalemia, hyponatremia
- 656 **Musculoskeletal:** *Less common:* joint swelling
- 657 *Infrequent:* sciatica, joint and muscle stiffness
- 658 *Rare:* avascular necrosis/hip osteonecrosis
- 659 **Nervous System/Psychiatric:** *Less common:* paresthesia
- 660 *Infrequent:* depression, anxiety, syncope, peripheral neuropathy, somnolence, migraine,
661 memory impairment
- 662 *Rare:* increased intracranial pressure, cerebral edema (including fatalities), confusion,
663 convulsions
- 664 **Renal:** *Infrequent:* renal failure, urinary frequency, hematuria
- 665 **Reproductive:** *Infrequent:* breast enlargement, menorrhagia, sexual dysfunction
- 666 **Respiratory:** *Rare:* interstitial pneumonitis, pulmonary fibrosis
- 667 **Special Senses:** *Less common:* conjunctivitis, vision blurred
- 668 *Infrequent:* conjunctival hemorrhage, dry eye, vertigo, tinnitus
- 669 *Rare:* macular edema, papilledema, retinal hemorrhage, glaucoma, vitreous hemorrhage
- 670 **Vascular Disorders:** *Rare:* thrombosis/embolism

671 OVERDOSAGE

672 Experience with doses greater than 800 mg is limited. Isolated cases of Gleevec[®] (imatinib
673 mesylate) overdose have been reported. In the event of overdosage, the patient should be
674 observed and appropriate supportive treatment given.

675 A patient with myeloid blast crisis experienced Grade 1 elevations of serum creatinine,
676 Grade 2 ascites and elevated liver transaminase levels, and Grade 3 elevations of bilirubin
677 after inadvertently taking 1,200 mg of Gleevec daily for 6 days. Therapy was temporarily
678 interrupted and complete reversal of all abnormalities occurred within 1 week. Treatment was
679 resumed at a dose of 400 mg daily without recurrence of adverse events. Another patient
680 developed severe muscle cramps after taking 1,600 mg of Gleevec daily for 6 days. Complete
681 resolution of muscle cramps occurred following interruption of therapy and treatment was
682 subsequently resumed. Another patient that was prescribed 400 mg daily, took 800 mg of
683 Gleevec on Day 1 and 1,200 mg on Day 2. Therapy was interrupted, no adverse events
684 occurred and the patient resumed therapy.

685 DOSAGE AND ADMINISTRATION

686 Therapy should be initiated by a physician experienced in the treatment of patients with
687 hematological malignancies or malignant sarcomas, as appropriate.

688 Ph+ CML

689 The recommended dosage of Gleevec[®] (imatinib mesylate) is 400 mg/day for adult
690 patients in chronic phase CML and 600 mg/day for adult patients in accelerated phase or blast
691 crisis. The recommended dosage of Gleevec for children with newly diagnosed Ph+ CML is
692 340 mg/m²/day (not to exceed 600 mg). The recommended Gleevec dosage is 260 mg/m²/day
693 for children with Ph+ chronic phase CML recurrent after stem cell transplant or who are
694 resistant to interferon-alpha therapy.

695 GIST

696 The recommended dosage of Gleevec is 400 mg/day or 600 mg/day for adult patients
697 with unresectable and/or metastatic, malignant GIST.

698

699 General Information

700 The prescribed dose should be administered orally, with a meal and a large glass of
701 water. Doses of 400 mg or 600 mg should be administered once daily, whereas a dose of
702 800 mg should be administered as 400 mg twice a day.

703 In children, Gleevec treatment can be given as a once-daily dose or alternatively the
704 daily dose may be split into two - once in the morning and once in the evening. There is no
705 experience with Gleevec treatment in children under 2 years of age.

706 Patients with mild and moderate hepatic impairment should be treated at a starting
707 dose of 400 mg/day. Patients with severe hepatic impairment should be treated at a starting
708 dose of 300 mg/day. (See CLINICAL PHARMACOLOGY and PRECAUTIONS)

709 For patients unable to swallow the film-coated tablets, the tablets may be dispersed in
710 a glass of water or apple juice. The required number of tablets should be placed in the
711 appropriate volume of beverage (approximately 50 mL for a 100-mg tablet, and 200 mL for a
712 400-mg tablet) and stirred with a spoon. The suspension should be administered immediately
713 after complete disintegration of the tablet(s).

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

716 In CML, a dose increase from 400 mg to 600 mg in adult patients with chronic phase
717 disease, or from 600 mg to 800 mg (given as 400 mg twice daily) in adult patients in
718 accelerated phase or blast crisis may be considered in the absence of severe adverse drug
719 reaction and severe non-leukemia related neutropenia or thrombocytopenia in the following
720 circumstances: disease progression (at any time), failure to achieve a satisfactory hematologic
721 response after at least 3 months of treatment, failure to achieve a cytogenetic response after
722 6-12 months of treatment, or loss of a previously achieved hematologic or cytogenetic
723 response.

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

727 For daily dosing of 800 mg and above, dosing should be accomplished using the
728 400-mg tablet to reduce exposure to iron.

729 **Dose Adjustment for Hepatotoxicity and Other Non-Hematologic Adverse** 730 **Reactions**

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

734 If elevations in bilirubin >3 x institutional upper limit of normal (IULN) or in liver
735 transaminases >5 x IULN occur, Gleevec should be withheld until bilirubin levels have
736 returned to a <1.5 x IULN and transaminase levels to <2.5 x IULN. In adults, treatment with
737 Gleevec may then be continued at a reduced daily dose (i.e., 400 mg to 300 mg, 600 mg to
738 400 mg or 800 mg to 600 mg). In children, daily doses can be reduced under the same
739 circumstances from 340 mg/m²/day to 260 mg/m²/day or from 260 mg/m²/day to 200
740 mg/m²/day .

741 **Dose Adjustment for Hematologic Adverse Reactions**

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

744

745

Table 10 Dose Adjustments for Neutropenia and Thrombocytopenia

<p>Chronic Phase CML (starting dose 400 mg)</p> <p>Or GIST (starting dose either 400 mg or 600 mg)</p>	<p>ANC $<1.0 \times 10^9/L$ and/or Platelets $<50 \times 10^9/L$</p>	<ol style="list-style-type: none"> 1. Stop Gleevec until ANC $\geq 1.5 \times 10^9/L$ and platelets $\geq 75 \times 10^9/L$ 2. Resume treatment with Gleevec at the original starting dose of 400 mg or 600 mg 3. If recurrence of ANC $<1.0 \times 10^9/L$ and/or platelets $<50 \times 10^9/L$, repeat step 1 and resume Gleevec at a reduced dose (300 mg if starting dose was 400 mg, 400 mg if starting dose was 600 mg)
<p>Newly diagnosed pediatric chronic phase CML [99] (start at dose 340 mg/m²)</p>	<p>ANC $< 1.0 \times 10^9/L$ and/or platelets $< 50 \times 10^9/L$</p>	<ol style="list-style-type: none"> 1 Stop Gleevec until ANC $\geq 1.5 \times 10^9/L$ and platelets $\geq 75 \times 10^9/L$ 2 Resume treatment with Gleevec at previous dose (i.e. before severe adverse reaction) 3. In the event of recurrence of ANC $< 1.0 \times 10^9/L$ and/or platelets $< 50 \times 10^9/L$, repeat step 1 and resume Gleevec at reduced dose of 260 mg/m² if the starting dose was 340 mg/m²
<p>Pediatric patients with Ph+ chronic phase CML recurrent after stem cell transplant or who are resistant to interferon-alpha therapy. (start at dose 260 mg/m²)</p>	<p>ANC $< 1.0 \times 10^9/L$ and/or platelets $< 50 \times 10^9/L$</p>	<ol style="list-style-type: none"> 1 Stop Gleevec until ANC $\geq 1.5 \times 10^9/L$ and platelets $\geq 75 \times 10^9/L$. 2. Resume treatment with Gleevec at previous dose (i.e. before severe adverse reaction) 3. In the event of recurrence of ANC $< 1.0 \times 10^9/L$ and/or platelets $< 50 \times 10^9/L$, repeat step 1 and resume Gleevec at reduced dose of 200 mg/m² if the starting dose was 260 mg/m²
<p>Ph+ CML : Accelerated Phase and Blast Crisis (starting dose 600 mg)</p>	<p>ANC $<0.5 \times 10^9/L$ and/or Platelets $<10 \times 10^9/L$</p>	<ol style="list-style-type: none"> 1. Check if cytopenia is related to leukemia (marrow aspirate or biopsy) 2. If cytopenia is unrelated to

		<p>leukemia, reduce dose of Gleevec to 400 mg</p> <p>3. If cytopenia persists 2 weeks, reduce further to 300 mg</p> <p>4. If cytopenia persists 4 weeks and is still unrelated to leukemia, stop Gleevec until ANC $\geq 1 \times 10^9/L$ and platelets $\geq 20 \times 10^9/L$ and then resume treatment at 300 mg</p>
--	--	---

746

747

748

749

750 **HOW SUPPLIED**

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

752 **100-mg Tablets**

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

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

756 **400-mg Tablets**

757 Very dark yellow to brownish orange, film-coated tablets, ovaloid, biconvex with bevelled
758 edges, debossed with “400” on one side with score on the other side, and “SL” on each side of
759 the score.

760 Bottles of 30 tablets.....NDC 0078-0438-15

761 **Storage**

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

764 Dispense in a tight container, USP.

765

766 REV: 2006

XXXXXXXX 2006

T2006-XX-XX

767

XXXXXX

768

769  **NOVARTIS**

770

771 Manufactured by:

Distributed by:

772 Novartis Pharma Stein AG
773 Stein, Switzerland
774
775
776 © Novartis
777

Novartis Pharmaceuticals Corporation
East Hanover, New Jersey 07936