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

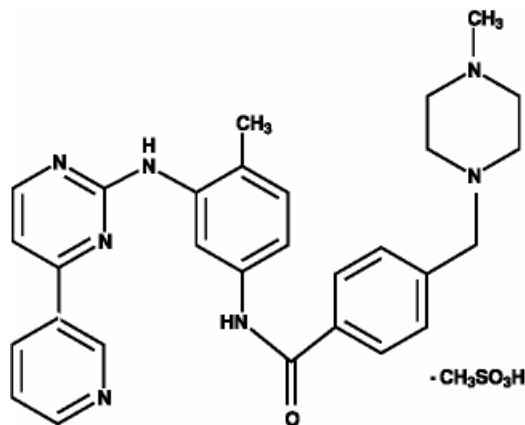
6 **Tablets**

7 **Rx only**

8 **Prescribing Information**

9 **DESCRIPTION**

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



14
15 Imatinib mesylate is a white to off-white to brownish or yellowish tinged crystalline
16 powder. Its molecular formula is C₂₉H₃₁N₇O • CH₄SO₃ and its molecular weight is 589.7.
17 Imatinib mesylate is soluble in aqueous buffers ≤ 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[®] (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-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 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.

60 Elimination is predominately in the feces, mostly as metabolites. Based on the
61 recovery of compound(s) after an oral ¹⁴C-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/m² in children vs. 10.0 L/hr/m² 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/m² and 340 mg/m² achieved
75 an AUC similar to the 400-mg dose in adults. The comparison of AUC₍₀₋₂₄₎ on Day 8 vs. Day
76 1 at 260 mg/m² and 340 mg/m² 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₍₀₋₂₄₎ and AUC_(0-∞) 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 μ 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***

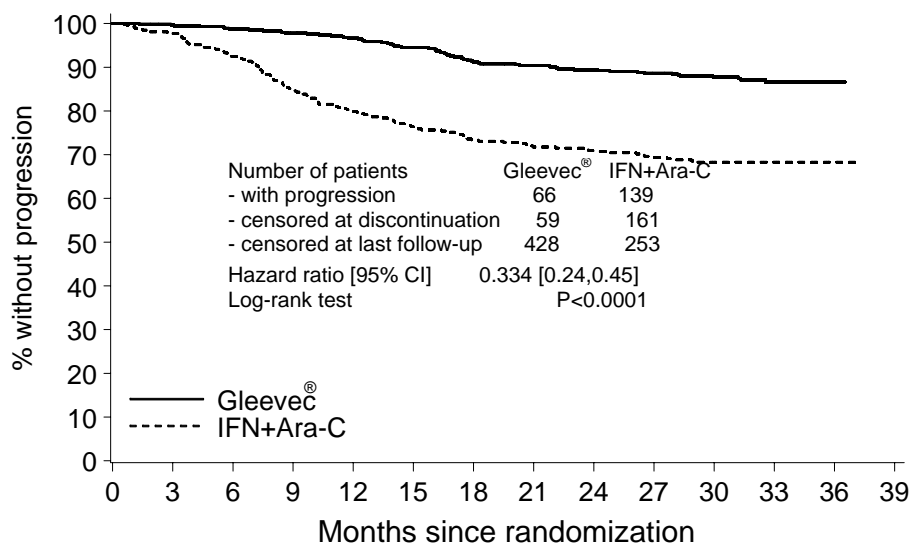
106 An open-label, multicenter, international randomized Phase 3 study has been conducted in
107 patients with newly diagnosed Philadelphia chromosome positive (Ph+) chronic myeloid
108 leukemia (CML) in chronic phase. This study compared treatment with either single-agent
109 Gleevec[®] (imatinib mesylate) 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/m²/day subcutaneously in combination with subcutaneous Ara-C
117 20 mg/m²/day for 10 days/month.

118 A total of 1106 patients were randomized from 177 centers in 16 countries, 553 to
119 each arm. Baseline characteristics were well balanced between the two arms. Median age was
120 51 years (range 18-70 years), with 21.9% of patients ≥60 years of age. There were 59% males
121 and 41% females; 89.9% Caucasian and 4.7% Black patients. With a median follow-up of 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 (≥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

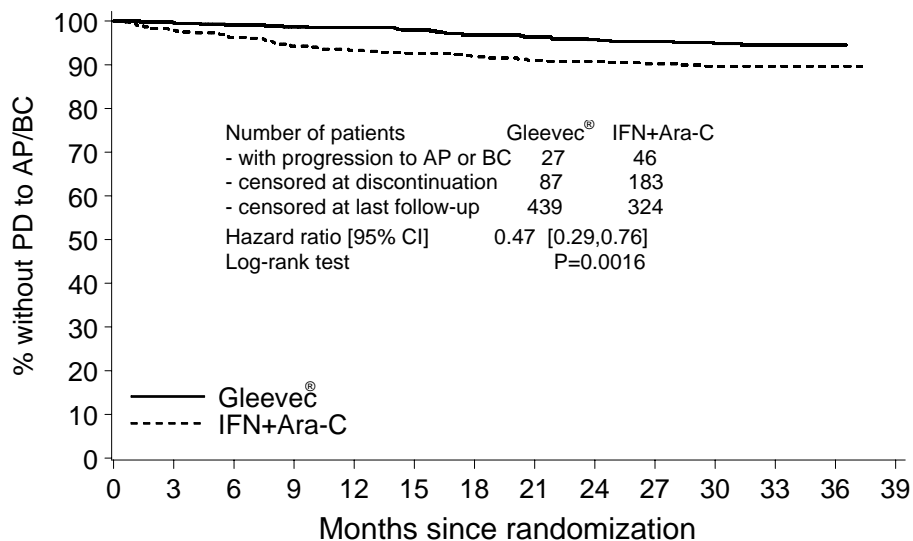
146 but without a major molecular response, and 82% in patients who were not in complete
 147 cytogenetic response at this time point ($p < 0.001$).

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.

158 **Table 1 Response in Newly Diagnosed CML Study (First-Line) (30-month data)**

159		Gleevec[®]	IFN+Ara-C
160	(Best Response Rate)	n=553	n=553
161	Hematologic Response¹		
162	CHR Rate n (%)	527 (95.3%)*	308 (55.7%)*
163	[95% CI]	[93.2%, 96.9%]	[51.4%, 59.9%]
164	Cytogenetic Response²		
165	Major Cytogenetic Response n (%)	461 (83.4%)*	90 (16.3%)*
166	[95% CI]	[80.0%, 86.4%]	[13.3%, 19.6%]
167	Unconfirmed ³	87.2%*	23.0%*
168	Complete Cytogenetic Response n (%)	378 (68.4%)*	30(5.4%)*
169	Unconfirmed ³	78.8%*	10.7%*
170	Molecular response⁴		
171	Major response at 12 months (%)	40%*	2%*

172 **Major response at 24 months (%)** 54%* NA⁵* p<0.001, Fischer's exact test

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

174 WBC<10 x 10⁹/L, platelet <450 x 10⁹/L, myelocyte + metamyelocyte <5% in blood, no blasts and
175 promyelocytes in blood, basophils <20%, no extramedullary involvement.

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

178 ³ Unconfirmed cytogenetic response is based on a single bone marrow cytogenetic evaluation,
179 therefore unconfirmed complete or partial cytogenetic responses might have had a lesser
180 cytogenetic response on a subsequent bone marrow evaluation.

181 ⁴ **Major molecular response criteria:** in the peripheral blood, after 12 months of therapy, reduction
182 of ≥3 logarithms in the amount of BCR-ABL transcripts (measured by real-time quantitative reverse
183 transcriptase PCR assay) over a standardized baseline.

184 ⁵ Not Applicable: insufficient data, only two patients available with samples

185

186 Physical, functional, and treatment-specific biologic response modifier scales from the
187 FACT-BRM (Functional Assessment of Cancer Therapy - Biologic Response Modifier)
188 instrument were used to assess patient-reported general effects of interferon toxicity in 1067
189 patients with CML in chronic phase. After one month of therapy to six months of therapy,
190 there was a 13%-21% decrease in median index from baseline in patients treated with
191 interferon, consistent with increased symptoms of interferon toxicity. There was no apparent
192 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 ≥ 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 ≥ 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 ≥ 12 months and 10% for ≥ 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**

	Chronic Phase IFN Failure (n=532)	Accelerated Phase (n=235)	Myeloid Blast Crisis (n=260)
		600 mg n=158	600 mg n=223
	400 mg	400 mg n=77	400 mg n=37
		% of patients [CI_{95%}]	
251	Hematologic Response¹	95% [92.3-96.3]	71% [64.8-76.8]
252			31% [25.2-36.8]
253	Complete Hematologic		
254	Response (CHR)	95%	38%
255	No Evidence of Leukemia (NEL)	Not applicable	13%
256	Return to Chronic		
257	Phase (RTC)	Not applicable	20%
258	Major Cytogenetic Response²	60% [55.3-63.8]	21% [16.2-27.1]
259	(Unconfirmed ³)	(65%)	(27%)
260	Complete ⁴ (Unconfirmed ³)	39% (47%)	16% (20%)
			2% (7%)

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

262 CHR: Chronic phase study [WBC <10 x 10⁹/L, platelet <450 x 10⁹/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 10⁹/L, platelets ≥100 x
265 10⁹/L, no blood blasts, BM blasts <5% and no extramedullary disease]

266 NEL: same criteria as for CHR but ANC ≥1 x 10⁹/L and platelets ≥20 x 10⁹/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 ² **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 ³ 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 ⁴ 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/m²/day (n=3), 340 mg/m²/day (n=4),
301 440 mg/m²/day (n=5) and 570 mg/m²/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/m²/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/m²/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	Total Patients	N	Confirmed Partial Response N (%)	95% Confidence Interval
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[®] (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[®] (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 ≥ 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 ≥ 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 ≤ 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 ≤ 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®
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)⁽¹⁾

531 532 533	Preferred Term	All Grades		CTC Grades 3/4	
		Gleevec® N=551 (%)	IFN+Ara-C N=533 (%)	Gleevec® N=551 (%)	IFN+Ara-C 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 ⁽¹⁾ 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 (≥10% of all patients**
567 **in any trial)⁽¹⁾**

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

614 ⁽¹⁾ All adverse events occurring in ≥10% of patients are listed regardless of suspected relationship to
615 treatment.

616 ⁽²⁾ 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 ≥ 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 (≥ 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**

647 648 649 650	CTC Grades	Gleevec® N=551 %		IFN+Ara-C N=533 %	
		Grade 3	Grade 4	Grade 3	Grade 4
651	Hematology Parameters				
652	- Neutropenia*	12.3	3.1	20.8	4.3
653	- Thrombocytopenia*	8.3	0.2	15.9	0.6
654	- Anemia	3.1	0.9	4.1	0.2
655	Biochemistry Parameters				
656	- Elevated Creatinine	0	0	0.4	0
657	- Elevated Bilirubin	0.7	0.2	0.2	0
658	- Elevated Alkaline				
659	Phosphatase	0.2	0	0.8	0
660	- Elevated SGOT (AST)	2.9	0.2	3.8	0.4
661	- Elevated SGPT (ALT)	3.1	0.4	5.6	0

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

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

664 665 666 667 668 669	Myeloid Blast	Accelerated		Chronic Phase,		IFN Failure	
		Crisis (n=260)		Phase (n=235)		(n=532)	
		600 mg n=223		600 mg n=158		400 mg	
		400 mg n=37		400 mg n=77		400 mg	
		%		%		%	
670	CTC Grades	Grade 3	Grade 4	Grade 3	Grade 4	Grade 3	Grade 4
671	Hematology Parameters						
672	- Neutropenia	16	48	23	36	27	9
673	- Thrombocytopenia	30	33	31	13	21	<1
674	- Anemia	42	11	34	7	6	1
675	Biochemistry Parameters						
676	- Elevated Creatinine	1.5	0	1.3	0	0.2	0
677	- Elevated Bilirubin	3.8	0	2.1	0	0.6	0
678	- Elevated Alkaline						
679	Phosphatase	4.6	0	5.5	0.4	0.2	0
680	- Elevated SGOT (AST)	1.9	0	3.0	0	2.3	0
681	- Elevated SGPT (ALT)	2.3	0.4	4.3	0	2.1	0

682
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
684 $\geq 10-50 \times 10^9/L$, grade 4 $< 10 \times 10^9/L$), anemia (hemoglobin $\geq 65-80$ g/L, grade 4 < 65 g/L), elevated
685 creatinine (grade 3 $> 3-6$ x upper limit normal range [ULN], grade 4 > 6 x ULN), elevated bilirubin (grade
686 3 $> 3-10$ x ULN, grade 4 > 10 x ULN), elevated alkaline phosphatase (grade 3 $> 5-20$ x ULN, grade 4 > 20
687 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[®] (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 (≥10% of all patients at either**
704 **dose)⁽¹⁾**

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	709	(n=73)	(n=74)	(n=73)	(n=74)
710	710	%	%	%	%
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 ⁽¹⁾ All adverse events occurring in ≥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	740	%		%	
741	741	Grade 3	Grade 4	Grade 3	Grade 4
742	Hematology Parameters				
743	- Anemia	3	0	4	1
744	- Thrombocytopenia	0	0	1	0
745	- Neutropenia	3	3	5	4
746	Biochemistry Parameters				
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 ≥ 0.5 - $1.0 \times 10^9/L$, grade 4 $< 0.5 \times 10^9/L$), thrombocytopenia (grade 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 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, SGOT or SGPT (grade 3 > 5 - 20 x ULN, grade 4 > 20 x 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[®] 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[®] (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/m²/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/m²/day to 340 mg/m²/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/m²/day to 200 mg/m²/day or from 340 mg/m²/day to 260 mg/m²/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 ⁹ /L	1. Stop Gleevec until ANC
872 (starting dose 400mg ¹)	and/or	≥1.5 x 10 ⁹ /L and
873	Platelets <50 x 10 ⁹ /L	platelets ≥75 x 10 ⁹ /L
874 or GIST		2. Resume treatment with
875 (starting dose either		Gleevec at the original
876 400 mg or 600 mg)		starting dose of 400 mg ¹
877		or 600 mg

878			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^2 if starting dose was 400 mg^1 , 400 mg if starting dose was 600 mg)
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885	Accelerated Phase	³ ANC $<0.5 \times 10^9/L$	1. Check if cytopenia is related to leukemia (marrow aspirate or biopsy)
886	CML and Blast Crisis	and/or	2. If cytopenia is unrelated to leukemia, reduce dose of Gleevec to 400 mg
887	(starting dose 600 mg)	Platelets $<10 \times 10^9/L$	3. If cytopenia persist 2 weeks, reduce further to 300 mg
888			4. If cytopenia persist 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 .
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899 ¹ or $260 \text{ mg}/\text{m}^2$ in children
 900 ² or $200 \text{ mg}/\text{m}^2$ in children
 901 ³occurring after at least 1 month of treatment

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 edges debossed with “NVR” on one side and “SA” with score on the other side.

906 Bottles of 100 tabletsNDC 0078-0401-05

908 **400 mg Tablets**

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

910 Bottles of 30 tabletsNDC 0078-0402-15

912 **Storage**

913 Store at $25 \text{ }^\circ\text{C}$ ($77 \text{ }^\circ\text{F}$); excursions permitted to $15 \text{ }^\circ\text{C}$ - $30 \text{ }^\circ\text{C}$ ($59 \text{ }^\circ\text{F}$ - $86 \text{ }^\circ\text{F}$) [see USP
 914 Controlled Room Temperature]. Protect from moisture.

915 Dispense in a tight container, USP.

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