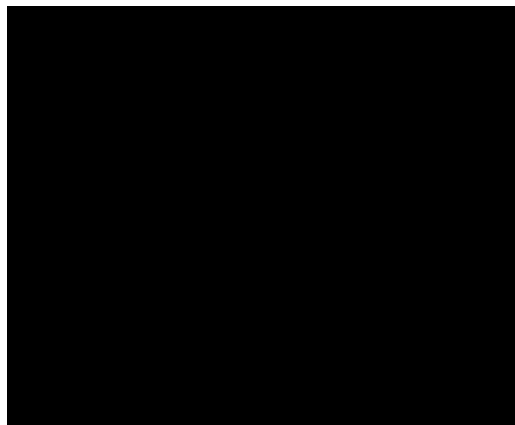


4 **Gleevec[®]**
5 **(imatinib mesylate)**6 **Tablets**7 **Rx only**8 **Prescribing Information**9 **DESCRIPTION**

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



14

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

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

25 CLINICAL PHARMACOLOGY

26 Mechanism of Action

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

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

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

40 Pharmacokinetics

41 The pharmacokinetics of Gleevec[®] (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- to
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 hr in adults). Dosing in children at both 260 mg/m² and 340 mg/m² achieved
76 an AUC similar to the 400-mg dose in adults. The comparison of AUC₍₀₋₂₄₎ on Day 8 vs. Day
77 1 at 260 mg/m² and 340 mg/m² dose levels revealed a 1.5- and 2.2-fold drug accumulation,
78 respectively, after repeated once-daily dosing. Mean imatinib AUC did not increase
79 proportionally with increasing dose.

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

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

86 **Drug-Drug Interactions**

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

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

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

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

104 CLINICAL STUDIES

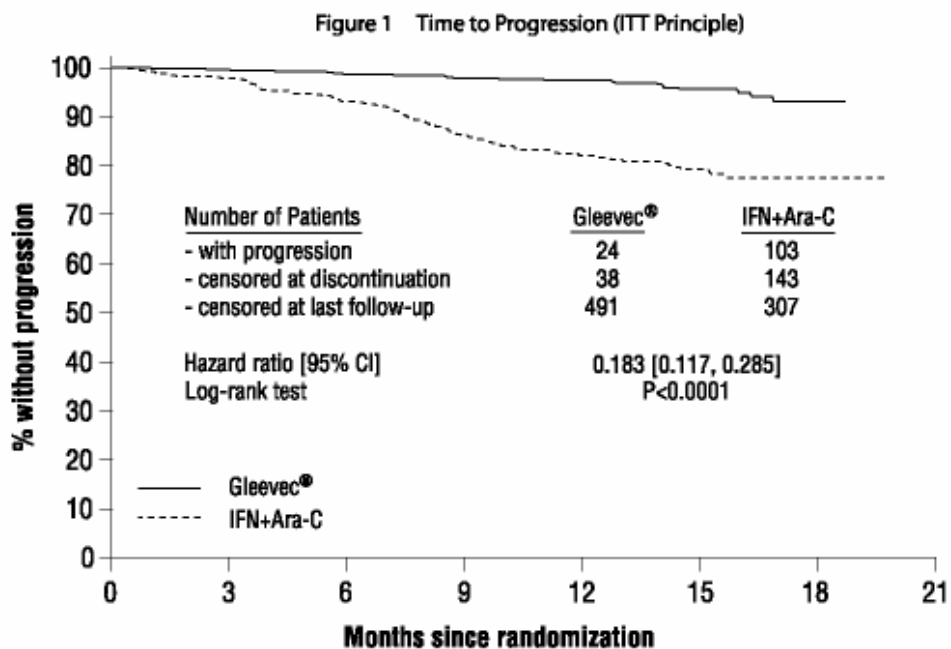
105 Chronic Myeloid Leukemia

106 *Chronic Phase, Newly Diagnosed*

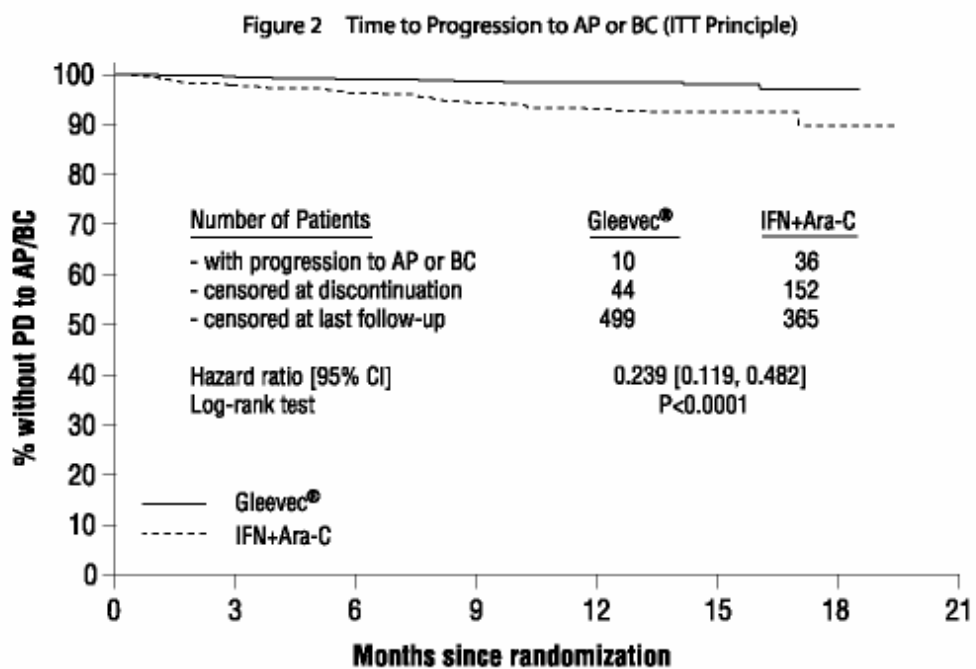
107 An open-label, multicenter, international randomized Phase 3 study has been conducted in
108 patients with newly diagnosed Philadelphia chromosome positive (Ph+) chronic myeloid
109 leukemia (CML) in chronic phase. This study compared treatment with either single-agent
110 Gleevec[®] (imatinib mesylate) or a combination of interferon-alfa (IFN) plus cytarabine
111 (Ara-C). Patients were allowed to cross over to the alternative treatment arm if they failed to
112 show a complete hematologic response (CHR) at 6 months, a major cytogenetic response
113 (MCyR) at 12 months, or if they lost a CHR or MCyR. Patients with increasing WBC or
114 severe intolerance to treatment were also allowed to cross over to the alternative treatment
115 arm with the permission of the study monitoring committee (SMC). In the Gleevec arm,
116 patients were treated initially with 400 mg daily. In the IFN arm, patients were treated with a
117 target dose of IFN of 5 MIU/m²/day subcutaneously in combination with subcutaneous Ara-C
118 20 mg/m²/day for 10 days/month.

119 A total of 1106 patients were randomized from 177 centers in 16 countries, 553 to
120 each arm. Baseline characteristics were well balanced between the two arms. Median age was
121 51 years (range 18-70 years), with 21.9% of patients ≥60 years of age. There were 59% males
122 and 41% females; 89.9% Caucasian and 4.7% Black patients. With a median follow-up of 14
123 and 13 months for Gleevec and IFN, respectively, 90% of patients randomized to Gleevec
124 were still receiving first-line treatment. Due to discontinuations and cross-overs, only 30% of
125 patients randomized to IFN were still on first-line treatment. In the IFN arm, withdrawal of
126 consent (13.4%) was the most frequent reason for discontinuation of first-line therapy, and the
127 most frequent reason for cross over to the Gleevec arm was severe intolerance to treatment
128 (22.8%).

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



146



147

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

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

(Best Response Rates)	Gleevec® n=553	IFN+Ara-C n=553
Hematologic Response¹		
CHR Rate n (%)	522 (94.4%)*	302 (54.6%)*
[95% CI]	[92.1%, 96.2%]	[50.4%, 58.8%]
Cytogenetic Response²		
Major Cytogenetic Response n (%)	419 (75.8%)*	67 (12.1%)*
[95% CI]	[72.0%, 79.3%]	[9.5%, 15.1%]
Unconfirmed ³	82.6%*	20.3%*
Complete Cytogenetic Response n (%)	297 (53.7%)*	15 (2.7%)*
Unconfirmed ³	67.8%*	7.4%*

165 * p<0.001, Fischer's exact test

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

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

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

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

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

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

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

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

188 532 patients were treated at a starting dose of 400 mg; dose escalation to 600 mg was allowed.
 189 The patients were distributed in three main categories according to their response to prior
 190 interferon: failure to achieve (within 6 months), or loss of a complete hematologic response

191 (29%), failure to achieve (within 1 year) or loss of a major cytogenetic response (35%), or
192 intolerance to interferon (36%). Patients had received a median of 14 months of prior IFN
193 therapy at doses $\geq 25 \times 10^6$ IU/week and were all in late chronic phase, with a median time
194 from diagnosis of 32 months. Effectiveness was evaluated on the basis of the rate of
195 hematologic response and by bone marrow exams to assess the rate of major cytogenetic
196 response (up to 35% Ph+ metaphases) or complete cytogenetic response (0% Ph+
197 metaphases). Median duration of treatment was 29 months with 81% of patients treated for
198 ≥ 24 months (maximum = 31.5 months). Efficacy results are reported in Table 2. Confirmed
199 major cytogenetic response rates were higher in patients with IFN intolerance (66%) and
200 cytogenetic failure (64%), than in patients with hematologic failure (47%). Hematologic
201 response was achieved in 98% of patients with cytogenetic failure, 94% of patients with
202 hematologic failure, and 92% of IFN-intolerant patients.

203 **Accelerated Phase**

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

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

217 **Myeloid Blast Crisis**

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

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

233 **Table 2 Response in CML Studies**

	Chronic Phase IFN Failure (n=532)	Accelerated Phase (n=235)	Myeloid Blast Crisis (n=260)
	400 mg	600 mg n=158 400 mg n=77	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) Return to Chronic Phase (RTC)	Not applicable	13%	5%
	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%)

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

250 CHR: Chronic phase study [WBC <10 x 10⁹/L, platelet <450 x 10⁹/L, myelocytes + metamyelocytes
251 <5% in blood, no blasts and promyelocytes in blood, basophils <20%, no extramedullary
252 involvement] and in the accelerated and blast crisis studies [ANC ≥1.5 x 10⁹/L, platelets ≥100 x
253 10⁹/L, no blood blasts, BM blasts <5% and no extramedullary disease]

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

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

258 BM=bone marrow, PB=peripheral blood

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

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

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

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

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

284 **Pediatric CML**

285 One open-label, single-arm study enrolled 14 pediatric patients with Ph⁺ chronic phase CML
286 recurrent after stem cell transplant or resistant to alpha interferon therapy. Patients ranged in
287 age from 3 to 20 years old; 3 were 3-11 years old, 9 were 12-18 years old, and 2 were >18
288 years old. Patients were treated at doses of 260 mg/m²/day (n=3), 340 mg/m²/day (n=4),
289 440 mg/m²/day (n=5) and 570 mg/m²/day (n=2). In the 13 patients for whom cytogenetic data
290 are available, 4 achieved a major cytogenetic response, 7 achieved a complete cytogenetic
291 response, and 2 had minimal cytogenetic response. At the recommended dose of
292 260 mg/m²/day, 2 of 3 patients achieved a complete cytogenetic response. Cytogenetic
293 response rate was similar at all dose levels.

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

296 **Gastrointestinal Stromal Tumors**

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

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

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

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

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

320 **INDICATIONS AND USAGE**

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

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

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

337 **CONTRAINDICATIONS**

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

340 **WARNINGS**

341 **Pregnancy**

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

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

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

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

361 **PRECAUTIONS**

362 **General**

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

371 ***Fluid Retention and Edema:*** Gleevec is often associated with edema and occasionally
372 serious fluid retention (see ADVERSE REACTIONS). Patients should be weighed and
373 monitored regularly for signs and symptoms of fluid retention. An unexpected rapid weight
374 gain should be carefully investigated and appropriate treatment provided. The probability of
375 edema was increased with higher Gleevec dose and age >65 years in the CML studies. Severe
376 superficial edema was reported in 0.9% of newly diagnosed CML patients taking Gleevec,
377 and in 2%-6% of other adult CML patients taking Gleevec. In addition, other severe fluid
378 retention (e.g., pleural effusion, pericardial effusion, pulmonary edema, and ascites) events
379 were reported in 2%-6% of other adult CML patients taking Gleevec. Severe superficial
380 edema and severe fluid retention (pleural effusion, pulmonary edema and ascites) were
381 reported in 1%-6% of patients taking Gleevec for GIST.

382 There have been post-marketing reports, including fatalities, of cardiac tamponade,
383 cerebral edema, increased intracranial pressure, and papilledema in patients with CML treated
384 with Gleevec.

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

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

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

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

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

416 **Drug Interactions**

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

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

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

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

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

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

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

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

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

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

447 *In vitro*, Gleevec inhibits acetaminophen O-glucuronidation (K_i value of 58.5 μ M) at
448 therapeutic levels. Systemic exposure to acetaminophen is expected to be increased when
449 coadministered with Gleevec. No specific studies in humans have been performed and caution
450 is recommended.

451 **Carcinogenesis, Mutagenesis, Impairment of Fertility**

452 ~~Carcinogenicity studies have not been performed with imatinib mesylate.~~

453 The urogenital tract from a 2-year carcinogenicity study in rats receiving doses of 15,
454 30 and 60 mg/kg/day of imatinib mesylate showed renal adenomas/carcinomas, urinary
455 bladder papillomas and papillomas/carcinomas of the preputial and clitoral gland. Evaluation
456 of other organs in the rats is ongoing.

457 The papilloma/carcinoma of the preputial/clitoral gland were noted at 30 and 60
458 mg/kg/day (approximately 0.5 to 4 times the human daily exposure at 400mg/day). The
459 kidney adenoma/carcinoma and the urinary bladder papilloma were noted at 60 mg/kg/day.
460 The no-effect levels (NOELs) for the various target organs with neoplastic lesions were 15
461 mg/kg/day for preputial and clitoral gland; and 30 mg/kg/day for kidney and urinary bladder.

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

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

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

478 Pregnancy**479 Pregnancy Category D. (See WARNINGS.)****480 Nursing Mothers**

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

490 Pediatric Use

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

494 Geriatric Use

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

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

505 ADVERSE REACTIONS**506 Chronic Myeloid Leukemia**

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

510 The most frequently reported drug-related adverse events were edema, nausea and
511 vomiting, muscle cramps, musculoskeletal pain, diarrhea and rash (Table 4 for newly
512 diagnosed CML, Table 5 for other CML patients). Edema was most frequently periorbital or
513 in lower limbs and was managed with diuretics, other supportive measures, or by reducing the

514 dose of Gleevec[®] (imatinib mesylate). (See DOSAGE AND ADMINISTRATION.) The
515 frequency of severe superficial edema was 0.9%-6%.

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

524 Adverse events, regardless of relationship to study drug, that were reported in at least
525 10% of the patients treated in the Gleevec studies are shown in Tables 4 and 5.

526 **Table 4 Adverse Experiences Reported in Newly Diagnosed CML Clinical Trial**
527 **(≥10% of all patients)⁽¹⁾**

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

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

559 **Table 5** Adverse Experiences Reported in Other CML Clinical Trials ($\geq 10\%$ of all patients
 560 in any trial)⁽¹⁾

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

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

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

611 **Hematologic Toxicity**

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

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

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

623 **Hepatotoxicity**

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

629 **Adverse Reactions in Pediatric Population**

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

633 **Adverse Effects in Other Subpopulations**

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

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

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

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

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

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	
	%		%		%	
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

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

681 **Gastrointestinal Stromal Tumors**

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

685 discontinued for adverse events in 6 patients (8%) in both dose levels studied. Superficial
 686 edema, most frequently periorbital or lower extremity edema, was managed with diuretics,
 687 other supportive measures, or by reducing the dose of Gleevec[®] (imatinib mesylate).
 688 (See DOSAGE AND ADMINISTRATION.) Severe (CTC grade 3/4) superficial edema was
 689 observed in 3 patients (2%), including face edema in one patient. Grade 3/4 pleural effusion
 690 or ascites was observed in 3 patients (2%).

691 Adverse events, regardless of relationship to study drug, that were reported in at least
 692 10% of the patients treated with Gleevec are shown in Table 8. No major differences were
 693 seen in the severity of adverse events between the 400-mg or 600-mg treatment groups,
 694 although overall incidence of diarrhea, muscle cramps, headache, dermatitis, and edema was
 695 somewhat higher in the 600-mg treatment group.

696 **Table 8 Adverse Experiences Reported in GIST Trial (≥10% of all patients at either**
 697 **dose)⁽¹⁾**

698 699 700 701 702	698 699 700 701 702	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)
703	703	%	%	%	%
703	Fluid Retention	71	76	6	3
704	- Superficial Edema	71	76	4	0
705	- Pleural Effusion or Ascites	6	4	1	3
706	Diarrhea	56	60	1	4
707	Nausea	53	56	3	3
708	Fatigue	33	38	1	0
709	Muscle Cramps	30	41	0	0
710	Abdominal Pain	37	37	7	3
711	Skin Rash	26	38	3	3
712	Headache	25	35	0	0
713	Vomiting	22	23	1	3
714	Musculoskeletal Pain	19	11	3	0
715	Flatulence	16	23	0	0
716	Any Hemorrhage	18	19	5	8
717	- Tumor Hemorrhage	1	4	1	4
718	- Cerebral Hemorrhage	1	0	1	0
719	- GI Tract Hemorrhage	6	4	4	1
720	Nasopharyngitis	12	14	0	0
721	Pyrexia	12	5	0	0
722	Insomnia	11	11	0	0
723	Back Pain	11	10	1	0
724	Lacrimation Increased	6	11	0	0
725	Upper Respiratory Tract Infection	6	11	0	0
726	Taste Disturbance	1	14	0	0

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

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

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

732	733	400 mg		600 mg	
		(n=73)		(n=74)	
734	735	%		%	
736	737	Grade 3	Grade 4	Grade 3	Grade 4
736	Hematology Parameters				
737	- Anemia	3	0	4	1
738	- Thrombocytopenia	0	0	1	0
739	- Neutropenia	3	3	5	4
740	Biochemistry Parameters				
741	- Elevated Creatinine	0	1	3	0
742	- Reduced Albumin	3	0	4	0
743	- Elevated Bilirubin	1	0	1	3
744	- Elevated Alkaline Phosphatase	0	0	1	0
745	- Elevated SGOT (AST)	3	0	1	1
746	- Elevated SGPT (ALT)	3	0	4	0

747 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
748 $\geq 10 - 50 \times 10^9/L$, grade 4 $< 10 \times 10^9/L$), anemia (grade 3 $\geq 65-80$ g/L, grade 4 < 65 g/L), elevated
749 creatinine (grade 3 $> 3-6$ x upper limit normal range [ULN], grade 4 > 6 x ULN), elevated bilirubin (grade
750 3 $> 3-10$ x ULN, grade 4 > 10 x ULN), elevated alkaline phosphatase, SGOT or SGPT (grade 3 $> 5-20$ x
751 ULN, grade 4 > 20 x ULN), albumin (grade 3 < 20 g/L)

752 Additional Data From Multiple Clinical Trials

753
754 The following less common (estimated 1%-10%), infrequent (estimated 0.1%-1%), and rare
755 (estimated less than 0.1%) adverse events have been reported during clinical trials of Gleevec.
756 These events are included based on clinical relevance.

757
758 **Cardiovascular:** *Infrequent:* cardiac failure, tachycardia, hypertension, hypotension, flushing,
759 peripheral coldness *Rare:* pericarditis

760
761 **Clinical Laboratory Tests:** *Infrequent:* blood CPK increased, blood LDH increased

762
763 **Dermatologic:** *Less common:* dry skin, alopecia *Infrequent:* exfoliative dermatitis, bullous
764 eruption, nail disorder, skin pigmentation changes, photosensitivity reaction, purpura,
765 psoriasis *Rare:* vesicular rash, Stevens-Johnson syndrome, acute generalized exanthematous
766 pustulosis

767
768 **Digestive:** *Less common:* abdominal distension, gastroesophageal reflux, mouth ulceration
769 *Infrequent:* gastric ulcer, gastroenteritis, gastritis *Rare:* colitis, ileus/intestinal obstruction,
770 pancreatitis

771
772 **General Disorders and Administration Site Conditions:** *Rare:* tumor necrosis

773

- 774 **Hematologic:** *Infrequent:* pancytopenia *Rare:* aplastic anemia
775
- 776 **Hypersensitivity:** *Rare:* angioedema
777
- 778 **Infections:** *Infrequent:* sepsis, herpes simplex, herpes zoster
779
- 780 **Metabolic and Nutritional:** *Infrequent:* hypophosphatemia, dehydration, gout, appetite
781 disturbances, weight decreased *Rare:* hyperkalemia, hyponatremia
782
- 783 **Musculoskeletal:** *Less common:* joint swelling *Infrequent:* sciatica, joint and muscle stiffness
784
- 785 **Nervous System/Psychiatric:** *Less common:* paresthesia *Infrequent:* depression, anxiety,
786 syncope, peripheral neuropathy, somnolence, migraine, memory impairment *Rare:* increased
787 intracranial pressure, cerebral edema (including fatalities), confusion, convulsions
788
- 789 **Renal:** *Infrequent:* renal failure, urinary frequency, hematuria
790
- 791 **Reproductive:** *Infrequent:* breast enlargement, menorrhagia, sexual dysfunction
792
- 793 **Respiratory:** *Rare:* interstitial pneumonitis, pulmonary fibrosis
794
- 795 **Special Senses:** *Less common:* conjunctivitis, vision blurred *Infrequent:* conjunctival
796 hemorrhage, dry eye, vertigo, tinnitus *Rare:* macular edema, papilledema, retinal
797 hemorrhage, glaucoma, vitreous hemorrhage
798
- 799 **Vascular Disorders:** *Rare:* thrombosis/embolism

800 OVERDOSAGE

801 Experience with doses greater than 800 mg is limited. In the event of overdosage, the patient
802 should be observed and appropriate supportive treatment given. An oral dose of
803 1200 mg/m²/day, approximately 2.5 times the human dose of 800 mg, based on body surface
804 area, was not lethal to rats following 14 days of administration. A dose of 3600 mg/m²/day,
805 approximately 7.5 times the human dose of 800 mg, was lethal to rats after 7-10
806 administrations, due to general deterioration of the animals with secondary degenerative
807 histological changes in many tissues.

808 DOSAGE AND ADMINISTRATION

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

811 The recommended dosage of Gleevec[®] (imatinib mesylate) is 400 mg/day for adult
812 patients in chronic phase CML and 600 mg/day for adult patients in accelerated phase or blast
813 crisis. The recommended Gleevec dosage is 260 mg/m²/day for children with Ph⁺ chronic
814 phase CML recurrent after stem cell transplant or who are resistant to interferon-alpha

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

817 The prescribed dose should be administered orally, with a meal and a large glass of
818 water. Doses of 400 mg or 600 mg should be administered once-daily, whereas a dose of
819 800 mg should be administered as 400 mg twice a day.

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

823 For patients unable to swallow the film-coated tablets, the tablets may be dispersed in
824 a glass of water or apple juice. The required number of tablets should be placed in the
825 appropriate volume of beverage (approximately 50 mL for a 100-mg tablet, and 200 mL for a
826 400-mg tablet) and stirred with a spoon. The suspension should be administered immediately
827 after complete disintegration of the tablet(s).

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

830 In CML, a dose increase from 400 mg to 600 mg in adult patients with chronic phase
831 disease, or from 600 mg to 800 mg (given as 400 mg twice daily) in adult patients in
832 accelerated phase or blast crisis may be considered in the absence of severe adverse drug
833 reaction and severe non-leukemia related neutropenia or thrombocytopenia in the following
834 circumstances: disease progression (at any time); failure to achieve a satisfactory
835 hematologic response after at least 3 months of treatment; failure to achieve a cytogenetic
836 response after 6-12 months of treatment; or loss of a previously achieved hematologic or
837 cytogenetic response. In children with chronic phase CML, daily doses can be increased under
838 circumstances similar to those leading to an increase in adult chronic phase disease, from
839 260 mg/m²/day to 340 mg/m²/day, as clinically indicated.

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

843 For daily dosing of 800 mg and above, dosing should be accomplished using the
844 400-mg tablet to reduce exposure to iron. Patients at a total dose of 1200 mg daily may have
845 an increased susceptibility to excess iron. If routine blood sampling indicates sustained
846 increases in iron levels, attempts to lower other sources of iron exposure should be
847 undertaken.

848 **Dose Adjustment for Hepatotoxicity and Other Non-Hematologic Adverse** 849 **Reactions**

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

853 If elevations in bilirubin >3 x institutional upper limit of normal (IULN) or in liver
854 transaminases >5 x IULN occur, Gleevec should be withheld until bilirubin levels have
855 returned to a <1.5 x IULN and transaminase levels to <2.5 x IULN. In adults, treatment with

856 Gleevec may then be continued at a reduced daily dose (i.e., 400 mg to 300 mg or 600 mg to
857 400 mg). In children, daily doses can be reduced under the same circumstances from
858 260 mg/m²/day to 200 mg/m²/day or from 340 mg/m²/day to 260 mg/m²/day, respectively.

859 Dose Adjustment for Hematologic Adverse Reactions

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

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

863 Chronic Phase CML 864 (starting dose 400mg ¹) 865 866 or GIST 867 (starting dose either 868 400 mg or 600 mg) 869 870 871 872 873 874 875 876	ANC <1.0 x 10 ⁹ /L and/or Platelets <50 x 10 ⁹ /L	<ol style="list-style-type: none"> 1. Stop Gleevec until ANC ≥1.5 x 10⁹/L and platelets ≥75 x 10⁹/L 2. Resume treatment with Gleevec at the original starting dose of 400 mg¹ or 600 mg 3. If recurrence of ANC <1.0 x 10⁹/L and/or platelets <50 x 10⁹/L, repeat step 1 and resume Gleevec at a reduced dose (300 mg² if starting dose was 400 mg¹, 400 mg if starting dose was 600 mg)
877 Accelerated Phase 878 CML and Blast Crisis 879 (starting dose 600 mg) 880 881 882 883 884 885 886 887 888 889 890	³ ANC <0.5 x 10 ⁹ /L and/or Platelets <10 x 10 ⁹ /L	<ol style="list-style-type: none"> 1. Check if cytopenia is related to leukemia (marrow aspirate or biopsy) 2. If cytopenia is unrelated to leukemia, reduce dose of Gleevec to 400 mg 3. If cytopenia persists 2 weeks, reduce further to 300 mg 4. If cytopenia persists 4 weeks and is still unrelated to leukemia, stop Gleevec until ANC ≥1 x 10⁹/L and platelets ≥20 x 10⁹/L and then resume treatment at 300 mg.

891 ¹ or 260 mg/m² in children

892 ² or 200 mg/m² in children

893 ³occurring after at least 1 month of treatment

894 HOW SUPPLIED

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

896 100 mg Tablets

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

899 Bottles of 100 tabletsNDC 0078-0401-05

900 **400 mg Tablets**

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

903 Bottles of 30 tabletsNDC 0078-0402-15

904 **Storage**

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

907 Dispense in a tight container, USP.

908

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911  **NOVARTIS**

912

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