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

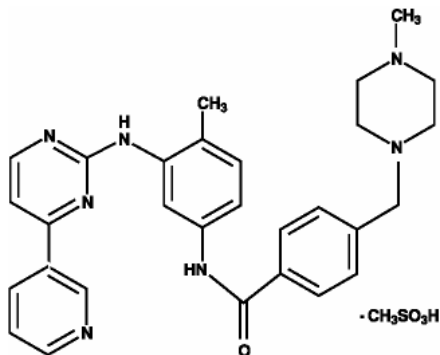
6 **Tablets**

7 **Rx only**

8 **Prescribing Information**

9 **DESCRIPTION**

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



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

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

25 CLINICAL PHARMACOLOGY

26 Mechanism of Action

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

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

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

40 Pharmacokinetics

41 The pharmacokinetics of Gleevec[®] (imatinib mesylate) have been evaluated in studies in
42 healthy subjects and in population pharmacokinetic studies in over 900 patients. Imatinib
43 is well absorbed after oral administration with C_{max} achieved within 2-4 hours post-dose. Mean
44 absolute bioavailability is 98%. Following oral administration in healthy volunteers, the
45 elimination half-lives of imatinib and its major active metabolite, the N-desmethyl derivative,
46 are approximately 18 and 40 hours, respectively. Mean imatinib AUC increases
47 proportionally with increasing doses ranging from 25 mg-1000 mg. There is no significant
48 change in the pharmacokinetics of imatinib on repeated dosing, and accumulation is 1.5-2.5
49 fold at steady state when Gleevec is dosed once daily. At clinically relevant concentrations of
50 imatinib, binding to plasma proteins in *in vitro* experiments is approximately 95%, mostly to
51 albumin and 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 = 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 μM, respectively. Gleevec is likely to increase the blood level of drugs
102 that are substrates of CYP2C9, CYP2D6 and CYP3A4/5. (See PRECAUTIONS.)

103 **CLINICAL STUDIES**

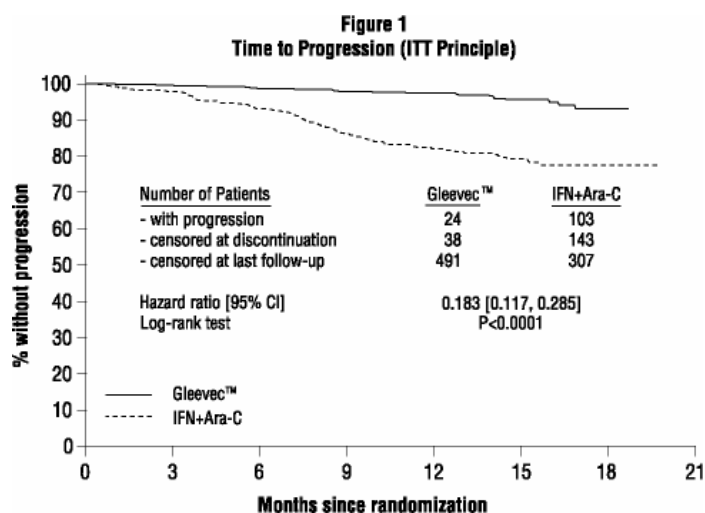
104 **Chronic Myeloid Leukemia**

105 ***Chronic Phase, Newly Diagnosed***

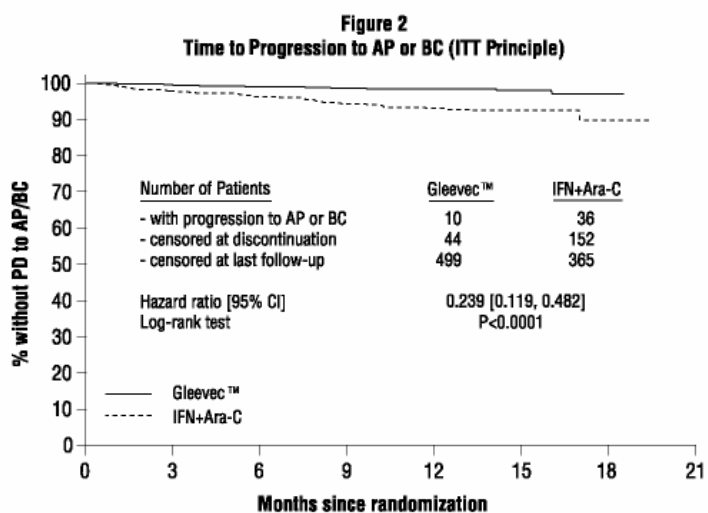
106 An open-label, multicenter, international randomized Phase 3 study has been conducted in
107 patients with newly diagnosed Philadelphia chromosome positive (Ph+) chronic myeloid
108 leukemia (CML) in chronic phase. This study compared treatment with either single-agent
109 Gleevec[®] (imatinib mesylate) or a combination of interferon-alfa (IFN) plus cytarabine
110 (Ara-C). Patients were allowed to cross over to the alternative treatment arm if they failed to
111 show a complete hematologic response (CHR) at 6 months, a major cytogenetic response
112 (MCyR) at 12 months, or if they lost a CHR or MCyR. Patients with increasing WBC or
113 severe intolerance to treatment were also allowed to cross over to the alternative treatment
114 arm with the permission of the study monitoring committee (SMC). In the Gleevec arm,
115 patients were treated initially with 400 mg daily. In the IFN arm, patients were treated with a
116 target dose of IFN of 5 MIU/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 14
122 and 13 months for Gleevec and IFN, respectively, 90% of patients randomized to Gleevec
123 were still receiving first-line treatment. Due to discontinuations and cross-overs, only 30% of
124 patients randomized to IFN were still on first-line treatment. In the IFN arm, withdrawal of
125 consent (13.4%) was the most frequent reason for discontinuation of first-line therapy, and the
126 most frequent reason for cross over to the Gleevec arm was severe intolerance to treatment
127 (22.8%).

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



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146



147
148 Major cytogenetic response, hematologic response, time to accelerated phase or blast
149 crisis and survival were main secondary endpoints. Response data are shown in Table 1.
150 Complete hematologic response, major cytogenetic response and complete cytogenetic
151 response were also statistically significantly higher in the Gleevec arm compared to the IFN +
152 Ara-C arm.

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

154	Gleevec[®]	IFN+Ara-C
155	n=553	n=553
156	(Best Response Rates)	
156	Hematologic Response¹	
157	CHR Rate n (%)	302 (54.6%)*
158	[95% CI]	[50.4%, 58.8%]
159	Cytogenetic Response²	
160	Major Cytogenetic Response n (%)	67 (12.1%)*
161	[95% CI]	[9.5%, 15.1%]
162	Unconfirmed ³	20.3%*
163	Complete Cytogenetic Response n (%)	15 (2.7%)*
164	Unconfirmed ³	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 ≥25 x 10⁶ 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)	Not applicable	13%	5%
Return to Chronic Phase (RTC)	Not applicable	20%	18%
Major Cytogenetic Response²	60% [55.3-63.8]	21% [16.2-27.1]	7% [4.5-11.2]
(Unconfirmed ³)	(65%)	(27%)	(15%)
Complete ⁴ (Unconfirmed ³)	39% (47%)	16% (20%)	2% (7%)

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

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

372

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

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

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

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

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

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

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

417 **Drug Interactions**

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

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

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

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

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

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

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

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

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

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

448 **Carcinogenesis, Mutagenesis, Impairment of Fertility**

449 Carcinogenicity studies have not been performed with imatinib mesylate.

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

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

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

466 **Pregnancy**

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

468 **Nursing Mothers**

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

478 **Pediatric Use**

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

482 **Geriatric Use**

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

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

493 **ADVERSE REACTIONS**494 **Chronic Myeloid Leukemia**

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

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

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

512 Adverse events, regardless of relationship to study drug, that were reported in at least
 513 10% of the patients treated in the Gleevec studies are shown in Tables 4 and 5.

514 **Table 4 Adverse Experiences Reported in Newly Diagnosed CML Clinical Trial**
 515 **(≥10% of all patients)⁽¹⁾**

	All Grades		CTC Grades 3/4	
	Gleevec [®]	IFN+Ara-C	Gleevec [™]	IFN+Ara-C

516
517

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

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

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

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

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

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

599 **Hematologic Toxicity**

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

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

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

611 **Hepatotoxicity**

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

617 **Adverse Reactions in Pediatric Population**

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

621 **Adverse Effects in Other Subpopulations**

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

627 **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

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

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

	Myeloid Blast		Accelerated		Chronic Phase,	
	Crisis (n=260)		Phase (n=235)		IFN Failure (n=532)	
	600 mg n=223		600 mg n=158		400 mg	
	400 mg n=37		400 mg n=77		%	
	%		%		%	
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

664 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)

669 **Gastrointestinal Stromal Tumors**

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

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

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

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

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

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

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

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

	400 mg (n=73) %		600 mg (n=74) %	
CTC Grades	Grade 3	Grade 4	Grade 3	Grade 4
Hematology Parameters				
- Anemia	3	0	4	1
- Thrombocytopenia	0	0	1	0
- Neutropenia	3	3	5	4
Biochemistry Parameters				
- Elevated Creatinine	0	1	3	0
- Reduced Albumin	3	0	4	0
- Elevated Bilirubin	1	0	1	3
- Elevated Alkaline Phosphatase	0	0	1	0
- Elevated SGOT (AST)	3	0	1	1
- Elevated SGPT (ALT)	3	0	4	0

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

740 **Additional Data From Multiple Clinical Trials**

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

745
746 **Cardiovascular:** *Infrequent:* cardiac failure, tachycardia, hypertension, hypotension, flushing,
747 peripheral coldness. *Rare:* pericarditis.

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

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

755
756 **Digestive:** *Less common:* abdominal distension, gastroesophageal reflux, mouth ulceration
757 *Infrequent:* gastric ulcer, gastroenteritis, gastritis *Rare:* colitis, ileus/intestinal obstruction,
758 pancreatitis

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760 **General Disorders and Administration Site conditions:** *Rare:* tumor necrosis

761

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

763

764 **Hypersensitivity:** *Rare:* angioedema

765

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

767

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

770

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

772

773 **Nervous System/Psychiatric:** *Less common:* paresthesia *Infrequent:* depression, anxiety,
774 syncope, peripheral neuropathy, somnolence, migraine, memory impairment *Rare:* increased
775 intracranial pressure, cerebral edema (including fatalities), [confusion](#), [convulsions](#)

776

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

778

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

780

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

782

783 **Special Senses:** *Less common:* conjunctivitis, vision blurred *Infrequent:* conjunctival
784 hemorrhage, dry eye, vertigo, tinnitus *Rare:* macular edema, papilledema, retinal
785 hemorrhage, [glaucoma](#), [vitreous hemorrhage](#)

786

787 **Vascular Disorders:** *Rare:* [thrombosis/embolism](#)

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788 OVERDOSAGE

789 Experience with doses greater than 800 mg is limited. In the event of overdose, the patient
790 should be observed and appropriate supportive treatment given. An oral dose of
791 1200 mg/m²/day, approximately 2.5 times the human dose of 800 mg, based on body surface
792 area, was not lethal to rats following 14 days of administration. A dose of 3600 mg/m²/day,
793 approximately 7.5 times the human dose of 800 mg, was lethal to rats after 7-10
794 administrations, due to general deterioration of the animals with secondary degenerative
795 histological changes in many tissues.

796 DOSAGE AND ADMINISTRATION

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

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

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

805 The prescribed dose should be administered orally, with a meal and a large glass of
806 water. Doses of 400 mg or 600 mg should be administered once daily, whereas a dose of
807 800 mg should be administered as 400 mg twice a day.

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

811 For patients unable to swallow the film-coated tablets, the tablets may be dispersed in
812 a glass of water or apple juice. The required number of tablets should be placed in the
813 appropriate volume of beverage (approximately 50 mL for a 100-mg tablet, and 200 mL for a
814 400-mg tablet) and stirred with a spoon. The suspension should be administered immediately
815 after complete disintegration of the tablet(s).

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

818 In CML, a dose increase from 400 mg to 600 mg in adult patients with chronic phase
819 disease, or from 600 mg to 800 mg (given as 400 mg twice daily) in adult patients in
820 accelerated phase or blast crisis may be considered in the absence of severe adverse drug
821 reaction and severe non-leukemia related neutropenia or thrombocytopenia in the following
822 circumstances: disease progression (at any time); failure to achieve a satisfactory
823 hematologic response after at least 3 months of treatment; failure to achieve a cytogenetic
824 response after 6-12 months of treatment; or loss of a previously achieved hematologic or
825 cytogenetic response. In children with chronic phase CML, daily doses can be increased under
826 circumstances similar to those leading to an increase in adult chronic phase disease, from
827 260 mg/m²/day to 340 mg/m²/day, as clinically indicated.

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

831 **Dose Adjustment for Hepatotoxicity and Other Non-Hematologic Adverse** 832 **Reactions**

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

836 If elevations in bilirubin >3 x institutional upper limit of normal (IULN) or in liver
837 transaminases >5 x IULN occur, Gleevec should be withheld until bilirubin levels have
838 returned to a <1.5 x IULN and transaminase levels to <2.5 x IULN. In adults, treatment with
839 Gleevec may then be continued at a reduced daily dose (i.e., 400 mg to 300 mg or 600 mg to
840 400 mg). In children, daily doses can be reduced under the same circumstances from
841 260 mg/m²/day to 200 mg/m²/day or from 340 mg/m²/day to 260 mg/m²/day, respectively.

842 Dose Adjustment for Hematologic Adverse Reactions

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

845 Table 10 Dose Adjustments for Neutropenia and Thrombocytopenia

846 Chronic Phase CML 847 (starting dose 400mg ¹) 848 849 or GIST 850 (starting dose either 851 400 mg or 600 mg) 852	ANC <1.0 x 10 ⁹ /L and/or Platelets <50 x 10 ⁹ /L	1. Stop Gleevec until ANC ≥1.5 x 10 ⁹ /L and platelets ≥75 x 10 ⁹ /L 2. Resume treatment with Gleevec at the original starting dose of 400 mg ¹ or 600 mg 3. If recurrence of ANC <1.0 x 10 ⁹ /L and/or platelets <50 x 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)
860 Accelerated Phase 861 CML and Blast Crisis 862 (starting dose 600 mg) 863 864 865 866 867 868 869 870 871 872 873	³ ANC <0.5 x 10 ⁹ /L and/or Platelets <10 x 10 ⁹ /L	1. Check if cytopenia is related to leukemia (marrow aspirate or biopsy) 2. If cytopenia is unrelated to leukemia, reduce dose of Gleevec to 400 mg 3. If cytopenia persist 2 weeks, reduce further to 300 mg 4. If cytopenia persist 4 weeks and is still unrelated to leukemia, stop Gleevec until ANC ≥1 x 10 ⁹ /L and platelets ≥20 x 10 ⁹ /L and then resume treatment at 300 mg.

874 ¹ or 260 mg/m² in children

875 ² or 200 mg/m² in children

876 ³occurring after at least 1 month of treatment

877 HOW SUPPLIED

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

879 100 mg Tablets

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

882 Bottles of 100 tabletsNDC 0078-0401-05

883 400 mg Tablets

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

886 Bottles of 30 tabletsNDC 0078-0402-15

887 **Storage**

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

890 Dispense in a tight container, USP.

891 T200

892 REV: Printed in U.S.A.

893  **NOVARTIS**

894

895 Manufactured by:
896 Novartis Pharma Stein AG
897 Stein, Switzerland

Distributed by:
Novartis Pharmaceuticals Corporation
East Hanover, New Jersey 07936

898

899

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