

4 **Gleevec[®]**

5 **(imatinib mesylate)**

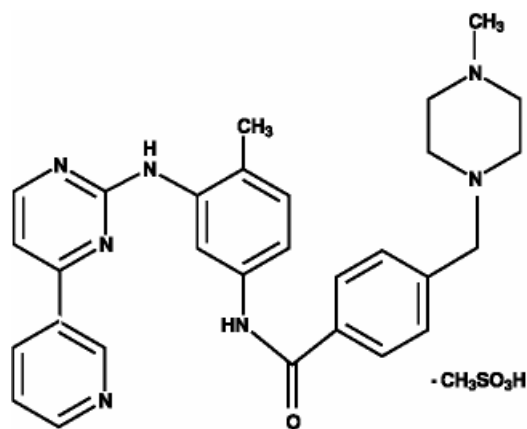
6 **Tablets**

7 **Rx only**

8 **Prescribing Information**

9 **DESCRIPTION**

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



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

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

25 CLINICAL PHARMACOLOGY

26 Mechanism of Action

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

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

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

40 Pharmacokinetics

41 The pharmacokinetics of Gleevec[®] (imatinib mesylate) have been evaluated in studies in
42 healthy subjects and in population pharmacokinetic studies in over 900 patients. Imatinib is
43 well absorbed after oral administration with C_{max} achieved within 2-4 hours post-dose. Mean
44 absolute bioavailability is 98%. Following oral administration in healthy volunteers, the
45 elimination half-lives of imatinib and its major active metabolite, the N-desmethyl derivative,
46 are approximately 18 and 40 hours, respectively. Mean imatinib AUC increases
47 proportionally with increasing doses ranging from 25 mg-1,000 mg. There is no significant
48 change in the pharmacokinetics of imatinib on repeated dosing, and accumulation is 1.5-
49 2.5-fold at steady state when Gleevec is dosed once daily. At clinically relevant
50 concentrations of imatinib, binding to plasma proteins in *in vitro* experiments is
51 approximately 95%, mostly to albumin and α_1 -acid glycoprotein.

52 The pharmacokinetics of Gleevec are similar in CML and GIST patients.

53 Metabolism and Elimination

54 CYP3A4 is the major enzyme responsible for metabolism of imatinib. Other cytochrome P450
55 enzymes, such as CYP1A2, CYP2D6, CYP2C9, and CYP2C19, play a minor role in its
56 metabolism. The main circulating active metabolite in humans is the N-demethylated
57 piperazine derivative, formed predominantly by CYP3A4. It shows *in vitro* potency similar to
58 the parent imatinib. The plasma AUC for this metabolite is about 15% of the AUC for
59 imatinib. The plasma protein binding of the N-demethylated metabolite CGP71588 is similar
60 to that of the parent compound.

61 Elimination is predominately in the feces, mostly as metabolites. Based on the
62 recovery of compound(s) after an oral ¹⁴C-labeled dose of imatinib, approximately 81% of the
63 dose was eliminated within 7 days, in feces (68% of dose) and urine (13% of dose).
64 Unchanged imatinib accounted for 25% of the dose (5% urine, 20% feces), the remainder
65 being metabolites.

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

71 **Special Populations**

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

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

91

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Table 1: Liver Function Classification

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

93 ULN=upper limit of normal for the institution

94

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

99 **Drug-Drug Interactions**

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

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

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

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

117 CLINICAL STUDIES

118 Chronic Myeloid Leukemia

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

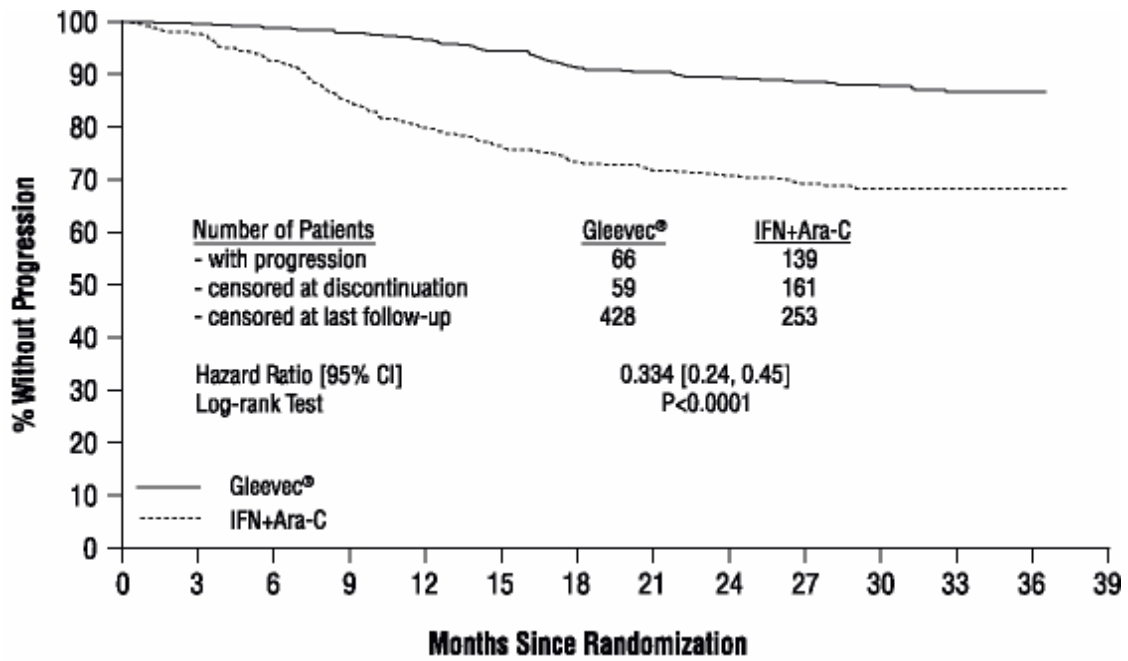
132 A total of 1,106 patients were randomized from 177 centers in 16 countries, 553 to
133 each arm. Baseline characteristics were well balanced between the two arms. Median age was
134 51 years (range 18-70 years), with 21.9% of patients ≥60 years of age. There were 59% males
135 and 41% females; 89.9%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

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

158 reduction in Bcr-Abl transcripts as measured by quantitative reverse transcriptase polymerase
 159 chain reaction) at 12 months, compared to 93% for patients in complete cytogenetic response
 160 but without a major molecular response, and 82% in patients who were not in complete
 161 cytogenetic response at this time point ($p < 0.001$).
 162

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Figure 1 Time to Progression (ITT)

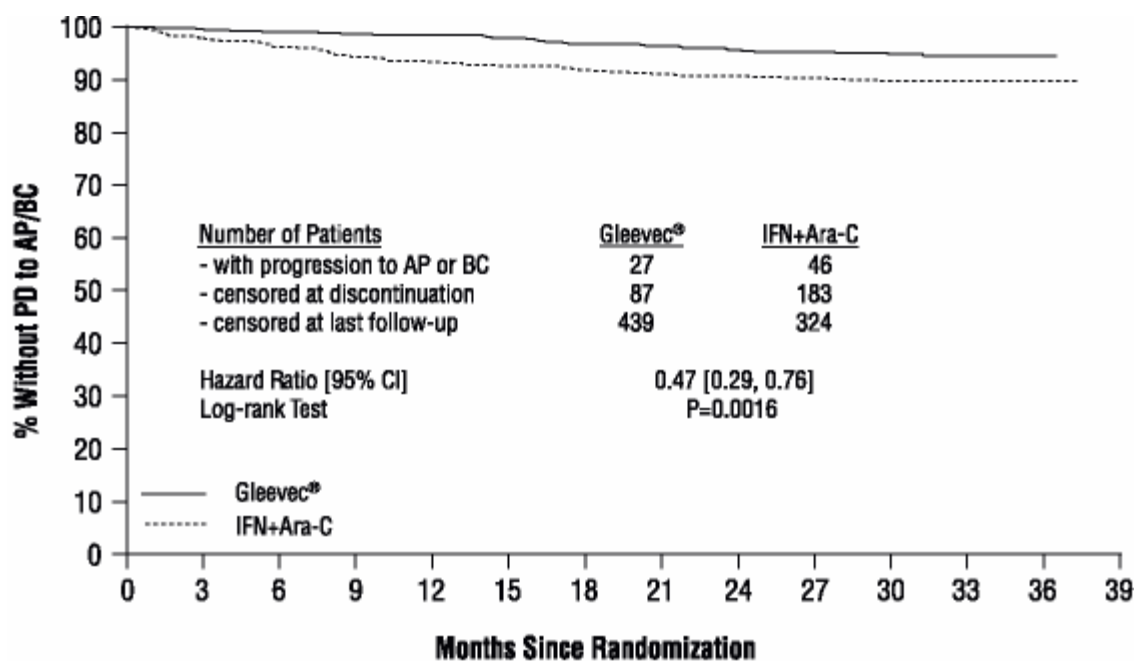


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Figure 2 Time to Progression to AP or BC (ITT)



167

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

173

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

	Gleevec® n=553	IFN+Ara-C n=553
(Best Response Rate)		
Hematologic Response¹		
CHR Rate n (%)	527 (95.3%)*	308 (55.7%)*
[95% CI]	[93.2%, 96.9%]	[51.4%, 59.9%]
Cytogenetic Response²		
Major Cytogenetic Response n (%)	461 (83.4%)*	90 (16.3%)*
[95% CI]	[80.0%, 86.4%]	[13.3%, 19.6%]
Unconfirmed ³	87.2%*	23.0%*
Complete Cytogenetic Response n (%)	378 (68.4%)*	30 (5.4%)*
Unconfirmed ³	78.8%*	10.7%*
Molecular Response⁴		
Major Response at 12 Months (%)	40%*	2%*
Major Response at 24 Months (%)	54%*	NA ⁵
* p<0.001, Fischer's exact test		

174

- 175 ¹ **Hematologic response criteria (all responses to be confirmed after ≥4 weeks):**
 176 WBC < 10 × 10⁹/L, platelet < 450 × 10⁹/L, myelocyte + metamyelocyte < 5% in blood, no blasts
 177 and promyelocytes in blood, basophils < 20%, no extramedullary involvement.
- 178 ² **Cytogenetic response criteria (confirmed after ≥4 weeks):** complete (0% Ph+ metaphases)
 179 or partial (1%-35%). A major response (0%-35%) combines both complete and partial responses.
- 180 ³ Unconfirmed cytogenetic response is based on a single bone marrow cytogenetic evaluation,
 181 therefore unconfirmed complete or partial cytogenetic responses might have had a lesser cytogenetic
 182 response on a subsequent bone marrow evaluation.
- 183 ⁴ **Major molecular response criteria:** in the peripheral blood, after 12 months of therapy,
 184 reduction of ≥3 logarithms in the amount of Bcr-Abl transcripts (measured by real-time quantitative
 185 reverse transcriptase PCR assay) over a standardized baseline.
- 186 ⁵ Not Applicable: insufficient data, only two patients available with samples
 187

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

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

201 ***Chronic Phase, Prior Interferon-Alpha Treatment:*** 532 patients were treated at a starting
 202 dose of 400 mg; dose escalation to 600 mg was allowed. The patients were distributed in three
 203 main categories according to their response to prior interferon: failure to achieve (within 6
 204 months), or loss of a complete hematologic response (29%), failure to achieve (within 1 year)
 205 or loss of a major cytogenetic response (35%), or intolerance to interferon (36%). Patients had
 206 received a median of 14 months of prior IFN therapy at doses ≥25 × 10⁶ IU/week and were all
 207 in late chronic phase, with a median time from diagnosis of 32 months. Effectiveness was
 208 evaluated on the basis of the rate of hematologic response and by bone marrow exams to
 209 assess the rate of major cytogenetic response (up to 35% Ph+ metaphases) or complete
 210 cytogenetic response (0% Ph+ metaphases). Median duration of treatment was 29 months
 211 with 81% of patients treated for ≥24 months (maximum = 31.5 months). Efficacy results are
 212 reported in Table 3. Confirmed major cytogenetic response rates were higher in patients with
 213 IFN intolerance (66%) and cytogenetic failure (64%), than in patients with hematologic
 214 failure (47%). Hematologic response was achieved in 98% of patients with cytogenetic
 215 failure, 94% of patients with hematologic failure, and 92% of IFN-intolerant patients.

216 ***Accelerated Phase:*** 235 patients with accelerated phase disease were enrolled. These patients
 217 met one or more of the following criteria: ≥15%-<30% blasts in PB or BM; ≥30% blasts +

218 promyelocytes in PB or BM; $\geq 20\%$ basophils in PB; and $< 100 \times 10^9/L$ platelets. The first 77
219 patients were started at 400 mg, with the remaining 158 patients starting at 600 mg.

220 Effectiveness was evaluated primarily on the basis of the rate of hematologic response,
221 reported as either complete hematologic response, no evidence of leukemia (i.e., clearance of
222 blasts from the marrow and the blood, but without a full peripheral blood recovery as for
223 complete responses), or return to chronic phase CML. Cytogenetic responses were also
224 evaluated. Median duration of treatment was 18 months with 45% of patients treated for ≥ 24
225 months (maximum=35 months). Efficacy results are reported in Table 3. Response rates in
226 accelerated phase CML were higher for the 600-mg dose group than for the 400-mg group:
227 hematologic response (75% vs. 64%), confirmed and unconfirmed major cytogenetic response
228 (31% vs. 19%).

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

234 Effectiveness was evaluated primarily on the basis of rate of hematologic response,
235 reported as either complete hematologic response, no evidence of leukemia, or return to
236 chronic phase CML using the same criteria as for the study in accelerated phase. Cytogenetic
237 responses were also assessed. Median duration of treatment was 4 months with 21% of
238 patients treated for ≥ 12 months and 10% for ≥ 24 months (maximum=35 months). Efficacy
239 results are reported in Table 3. The hematologic response rate was higher in untreated patients
240 than in treated patients (36% vs. 22%, respectively) and in the group receiving an initial dose
241 of 600 mg rather than 400 mg (33% vs. 16%). The confirmed and unconfirmed major
242 cytogenetic response rate was also higher for the 600-mg dose group than for the 400-mg dose
243 group (17% vs. 8%).

244

Table 3 Response in CML Studies

	Chronic Phase IFN Failure (n=532)	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%)

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

246 CHR: Chronic phase study [WBC <10 x 10⁹/L, platelet <450 x 10⁹/L, myelocytes + metamyelocytes
247 <5% in blood, no blasts and promyelocytes in blood, basophils <20%, no extramedullary
248 involvement] and in the accelerated and blast crisis studies [ANC ≥1.5 x 10⁹/L, platelets ≥100 x
249 10⁹/L, no blood blasts, BM blasts <5% and no extramedullary disease]

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

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

254 BM=bone marrow, PB=peripheral blood

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

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

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

263

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

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

282 **Pediatric CML:** A total of 51 pediatric patients with newly diagnosed and untreated CML in
283 chronic phase were enrolled in an open-label, multicenter, single arm phase 2 trial. Patients
284 were treated with Gleevec 340 mg/m²/day, with no interruptions in the absence of dose
285 limiting toxicity. Complete hematologic response (CHR) was observed in 78% of patients
286 after 8 weeks of therapy. The complete cytogenetic response rate (CCyR) was 65%,

287 comparable to the results observed in adults. Additionally, partial cytogenetic response
 288 (PCyR) was observed in 16%. The majority of patients who achieved a CCyR developed the
 289 CCyR between months 3 and 10 with a median time to response based on the Kaplan-Meier
 290 estimate of 6.74 months.

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

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

300 **Acute Lymphoblastic Leukemia**

301 A total of 48 Philadelphia chromosome positive acute lymphoblastic leukemia (Ph+ ALL)
 302 patients with relapsed/refractory disease were studied, 43 of whom received the recommended
 303 Gleevec dose of 600 mg/day. In addition 2 patients with relapsed/refractory Ph+ ALL
 304 received Gleevec 600 mg/day in a phase 1 study.

305 Hematologic and cytogenetic response rates for the 43 relapsed/refractory Ph+ALL phase 2
 306 study patients and for the 2 phase 1 patients are shown in Table 4. The median duration of
 307 hematologic response was 3.4 months and the median duration of MCyR was 2.3 months.

308

309 Table 4: Effect of Gleevec on relapsed/refractory Ph+ ALL.

	Phase 2 Study (N=43)	Phase 1 Study (N=2)
CHR	8 (19%)	2 (100%)
NEL	5 (12%)	
RTC/PHR	11 (26%)	
MCyR	15 (35%)	
CCyR	9 (21%)	
PCyR	6 (14%)	

310

311 **Myelodysplastic / Myeloproliferative diseases**

312 An open label, multicenter, phase 2 clinical trial was conducted testing Gleevec in diverse
 313 populations of patients suffering from life-threatening diseases associated with Abl, Kit or
 314 PDGFR protein tyrosine kinases. This study included 7 patients with MDS/MPD. These

315 patients were treated with Gleevec 400 mg daily. The ages of the enrolled patients ranged
 316 from 20 to 86 years. A further 24 patients with MDS/MPD aged 2 to 79 years were reported
 317 in 12 published case reports and a clinical study. These patients also received Gleevec at a
 318 dose of 400 mg daily with the exception of three patients who received lower doses. Of the
 319 total population of 31 patients treated for MDS/MPD, 14 (45%) achieved a complete
 320 hematological response and 12 (39%) a major cytogenetic response (including 10 with a
 321 complete cytogenetic response). Sixteen patients had a translocation, involving chromosome
 322 5q33 or 4p12, resulting in a PDGFR gene re-arrangement. All of these patients responded
 323 hematologically (13 completely). Cytogenetic response was evaluated in 12 out of 14 patients,
 324 all of whom responded (10 patients completely). Only 1(7%) out of the 14 patients without a
 325 translocation associated with PDGFR gene re-arrangement achieved a complete
 326 hematological response and none achieved a major cytogenetic response. A further patient
 327 with a PDGFR gene re-arrangement in molecular relapse after bone marrow transplant
 328 responded molecularly. Median duration of therapy was 12.9 months (0.8-26.7) in the 7
 329 patients treated within the phase 2 study and ranged between 1 week and more than 18 months
 330 in responding patients in the published literature. Results are provided in table 5. Response
 331 durations of phase 2 study patients ranged from 141+ days to 457+ days.

332

333

Table 5 Response in MDS/MPD

	N	Complete hematological response	Major Cytogenetic response
		N (%)	N (%)
Overall population	31	14 (45)	12 (39)
Chromosome 5 translocation	14	11 (79)	11 (79)
Chromosome 4 translocation	2	2 (100)	1 (50)
Others / no translocation	14	1 (7)	0 (0)
Molecular relapse	1	NE	NE

NE: Not evaluable

334 **Aggressive Systemic Mastocytosis**

335 One open-label, multicenter, phase 2 study was conducted testing Gleevec in diverse
 336 populations of patients suffering from life-threatening diseases associated with Abl, Kit or
 337 PDGFR protein tyrosine kinases. This study included 5 patients with aggressive systemic
 338 mastocytosis (ASM). The ASM patients were treated with 100 mg to 400 mg of Gleevec
 339 daily. These 5 patients ranged from 49 to 74 years of age. In addition to these 5 patients, 10
 340 published case reports and case series describe the use of Gleevec in 23 additional patients
 341 with ASM aged 26 to 85 years. These 23 patients also received 100 mg to 400 mg of Gleevec
 342 daily.

343 Cytogenetic abnormalities were evaluated in 20 of the 28 ASM patients treated with Gleevec
 344 from the published reports and in the phase 2 study. Seven of these 20 patients had the
 345 FIP1L1-PDGFR α fusion kinase (or CHIC2 deletion). Patients with this cytogenetic abnormality
 346 were predominantly males and had eosinophilia associated with their systemic mast cell
 347 disease. Two patients had a Kit mutation in the juxtamembrane region (one Phe522Cys and
 348 one K509I) and four patients had a D816V c-Kit mutation (not considered sensitive to
 349 Gleevec), one with concomitant CML.

350 Of the total population of 28 patients treated for ASM, 8 (29%) achieved a complete
 351 hematologic response and 9 (32%) a partial hematologic response (61% overall response
 352 rate). Median duration of Gleevec therapy for the 5 ASM patients in the phase 2 study was
 353 13 months (range 1.4-22.3 months) and between 1 month and more than 30 months in the
 354 responding patients described in the published medical literature. A summary of the response
 355 rates to Gleevec in ASM is provided in Table 6. Response durations of literature patients
 356 ranged from 1+ to 30+ months.

357 **Table 6 Response in ASM**

Cytogenetic abnormality	Number of patients	Complete hematologic response	Partial hematologic response
		N (%)	N (%)
FIP1L1-PDGFR α fusion kinase (or CHIC2 deletion)	7	7(100%)	0
Juxtamembrane mutation	2	0 (0%)	2 (100%)
Unknown or no cytogenetic abnormality detected	15	0(0%)	7 (44%)
D816V mutation	4	1* (25%)	0
Total	28	8 (29%)	9 (32%)

*Patient had concomitant CML and ASM

358

359 Gleevec has not been shown to be effective in patients with less aggressive forms of systemic
 360 mastocytosis (SM). Gleevec is therefore not recommended for use in patients with cutaneous
 361 mastocytosis, indolent systemic mastocytosis (smoldering SM or isolated bone marrow
 362 mastocytosis), SM with an associated clonal hematological non-mast cell lineage disease,
 363 mast cell leukemia, mast cell sarcoma or extracutaneous mastocytoma. Patients that harbor the
 364 D816V mutation of c-Kit are not sensitive to Gleevec and should not receive Gleevec.

365 **Hypereosinophilic Syndrome / Chronic Eosinophilic Leukemia**

366 One open-label, multicenter, phase 2 study was conducted testing Gleevec in diverse
 367 populations of patients suffering from life-threatening diseases associated with Abl, Kit or
 368 PDGFR protein tyrosine kinases. This study included 14 patients with Hypereosinophilic

369 Syndrome/Chronic Eosinophilic Leukemia (HES/CEL). HES patients were treated with
 370 100 mg to 1000 mg of Gleevec daily. The ages of these patients ranged from 16 to 64 years. A
 371 further 162 patients with HES/CEL aged 11 to 78 years were reported in 35 published case
 372 reports and case series. These patients received Gleevec at doses of 75 mg to 800 mg daily.
 373 Hematologic response rates are summarized in Table 7. Response durations for literature
 374 patients ranged from 6+ weeks to 44 months.

375 **Table 7 Response in HES/CEL**

Cytogenetic abnormality	Number of patients	Complete hematological response N (%)	Partial hematological response N (%)
Positive FIP1L1-PDGFR α fusion kinase	61	61 (100%)	0
Negative FIP1L1-PDGFR α fusion kinase	56	12 (21%)	9 (16%)
Unknown cytogenetic abnormality	59	34 (58%)	7 (12%)
Total	176	107 (61%)	23 (13%)

376

377 **Dermatofibrosarcoma Protuberans**

378 Dermatofibrosarcoma Protuberans (DFSP) is a cutaneous soft tissue sarcoma. It is
 379 characterized by a translocation of chromosomes 17 and 22. This translocation results in the
 380 fusion of 2 genes, the collagen type 1 alpha 1 gene and the PDGF B gene.

381 An open label, multicenter, phase 2 study was conducted testing Gleevec in a diverse
 382 population of patients suffering from life-threatening diseases associated with Abl, Kit or
 383 PDGFR protein tyrosine kinases. This study included 12 patients with DFSP who were
 384 treated with Gleevec 800 mg daily. The age of the DFSP patients ranged from 23 to 75 years;
 385 DFSP was metastatic, locally recurrent following initial surgical resection and not considered
 386 amenable to further surgery at the time of study entry. A further 6 DFSP patients treated with
 387 Gleevec are reported in 5 published case reports, their ages ranging from 18 months to 49
 388 years. The total population treated for DFSP therefore comprises 18 patients, 8 of them with
 389 metastatic disease. The adult patients reported in the published literature were treated with
 390 either 400 mg (4 cases) or 800 mg (1 case) Gleevec daily. A single pediatric patient received
 391 400 mg/m²/daily, subsequently increased to 520 mg/m²/daily. Ten patients had the PDGF B
 392 gene rearrangement, 5 had no available cytogenetics and 3 had complex cytogenetic
 393 abnormalities. Responses to treatment are described in Table 8.

394 **Table 8 Response in DFSP**

	Number of patients (n=18)	%
Complete response	7	39
Partial response *	8	44
Total responders	15	83

* 5 patients made disease free by surgery

395 Twelve of these 18 patients either achieved a complete response (7 patients) or were made
 396 disease free by surgery after a partial response (5 patients, including one child) for a total
 397 complete response rate of 67%. A further 3 patients achieved a partial response, for an overall
 398 response rate of 83%. Of the 8 patients with metastatic disease, five responded (62%), three of
 399 them completely (37%). For the 10 study patients with the PDGF B gene rearrangement there
 400 were 4 complete and 6 partial responses. The median duration of response in the phase 2
 401 study was 6.2 months, with a maximum duration of 24.3 months, while in the published
 402 literature it ranged between 4 weeks and more than 20 months.

403 **Gastrointestinal Stromal Tumors**

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

413 The primary outcome of the study was objective response rate. Tumors were required
 414 to be measurable at entry in at least one site of disease, and response characterization was
 415 based on Southwestern Oncology Group (SWOG) criteria. Results are shown in Table 9.

416 **Table 9 Tumor Response in GIST Trial**

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

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

421

422 **INDICATIONS AND USAGE**

423 Gleevec[®] (imatinib mesylate) is indicated for the treatment of:

- 424 • Newly diagnosed adult and pediatric patients with Philadelphia chromosome positive
425 chronic myeloid leukemia (Ph⁺ CML) in chronic phase. Follow-up is limited.
- 426 • Patients with Philadelphia chromosome positive chronic myeloid leukemia (Ph⁺
427 CML) in blast crisis, accelerated phase, or in chronic phase after failure of interferon-
428 alpha therapy. Gleevec is also indicated for the treatment of pediatric patients with
429 Ph⁺ chronic phase CML whose disease has recurred after stem cell transplant or who
430 are resistant to interferon-alpha therapy. There are no controlled trials in pediatric
431 patients demonstrating a clinical benefit, such as improvement in disease-related
432 symptoms or increased survival.
- 433 • Adult patients with relapsed or refractory Philadelphia chromosome positive acute
434 lymphoblastic leukemia (Ph⁺ ALL).
- 435 • Adult patients with myelodysplastic/ myeloproliferative diseases (MDS/MPD)
436 associated with PDGFR (platelet-derived growth factor receptor) gene re-
437 arrangements.
- 438 • Adult patients with aggressive systemic mastocytosis (ASM) without the D816V c-
439 Kit mutation or with c-Kit mutational status unknown.
- 440 • Adult patients with hypereosinophilic syndrome (HES) and/or chronic eosinophilic
441 leukemia (CEL) who have the FIP1L1-PDGFR α fusion kinase (mutational analysis or
442 FISH demonstration of CHIC2 allele deletion) and for patients with HES and/or CEL
443 who are FIP1L1-PDGFR α fusion kinase negative or unknown.
- 444 • Adult patients with unresectable, recurrent and/or metastatic dermatofibrosarcoma
445 protuberans (DFSP).
- 446 • Patients with Kit (CD117) positive unresectable and/or metastatic malignant
447 gastrointestinal stromal tumors (GIST). (See CLINICAL STUDIES, Gastrointestinal
448 Stromal Tumors.) The effectiveness of Gleevec in GIST is based on objective
449 response rate (see CLINICAL STUDIES). There are no controlled trials
450 demonstrating a clinical benefit, such as improvement in disease-related symptoms or
451 increased survival.

452 **CONTRAINDICATIONS**

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

455 **WARNINGS**

456 **Pregnancy**

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

458 Imatinib mesylate was teratogenic in rats when administered during organogenesis at
459 doses \geq 100 mg/kg, approximately equal to the maximum clinical dose of 800 mg/day based

460 on body surface area. Teratogenic effects included exencephaly or encephalocele,
461 absent/reduced frontal and absent parietal bones. Female rats administered doses ≥ 45 mg/kg
462 (approximately one-half the maximum human dose of 800 mg/day based on body surface
463 area) also experienced significant post-implantation loss as evidenced by either early fetal
464 resorption or stillbirths, nonviable pups and early pup mortality between postpartum Days 0
465 and 4. At doses higher than 100 mg/kg, total fetal loss was noted in all animals. Fetal loss was
466 not seen at doses ≤ 30 mg/kg (one-third the maximum human dose of 800 mg).

467 Male and female rats were exposed *in utero* to a maternal imatinib mesylate dose of
468 45 mg/kg (approximately one-half the maximum human dose of 800 mg) from Day 6 of
469 gestation and through milk during the lactation period. These animals then received no
470 imatinib exposure for nearly 2 months. Body weights were reduced from birth until terminal
471 sacrifice in these rats. Although fertility was not affected, fetal loss was seen when these male
472 and female animals were then mated.

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

476 PRECAUTIONS

477 General

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

486 ***Fluid Retention and Edema:*** Gleevec is often associated with edema and occasionally
487 serious fluid retention (see ADVERSE REACTIONS). Patients should be weighed and
488 monitored regularly for signs and symptoms of fluid retention. An unexpected rapid weight
489 gain should be carefully investigated and appropriate treatment provided. The probability of
490 edema was increased with higher Gleevec dose and age >65 years in the CML studies. Severe
491 superficial edema was reported in 1.1% of newly diagnosed CML patients taking Gleevec,
492 and in 2%-6% of other adult CML patients taking Gleevec. In addition, other severe fluid
493 retention (e.g., pleural effusion, pericardial effusion, pulmonary edema, and ascites) events
494 were reported in 0.7% of newly diagnosed CML patients taking Gleevec, and in 2%-6% of
495 other adult CML patients taking Gleevec. Severe superficial edema and severe fluid retention
496 (pleural effusion, pulmonary edema and ascites) were reported in 1%-6% of patients taking
497 Gleevec for GIST.

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

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

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

509 ***Hematologic Toxicity:*** Treatment with Gleevec is associated with anemia, neutropenia, and
510 thrombocytopenia. Complete blood counts should be performed weekly for the first month,
511 biweekly for the second month, and periodically thereafter as clinically indicated (for
512 example, every 2-3 months). In CML, the occurrence of these cytopenias is dependent on the
513 stage of disease and is more frequent in patients with accelerated phase CML or blast crisis
514 than in patients with chronic phase CML. In pediatric CML patients the most frequent
515 toxicities observed were grade 3 or 4 cytopenias including neutropenia, thrombocytopenia and
516 anemia. These generally occur within the first several months of therapy. (See DOSAGE
517 AND ADMINISTRATION.)

518 ***Hepatotoxicity:*** Hepatotoxicity, occasionally severe, may occur with Gleevec (see
519 ADVERSE REACTIONS). Liver function (transaminases, bilirubin, and alkaline
520 phosphatase) should be monitored before initiation of treatment and monthly, or as clinically
521 indicated. Laboratory abnormalities should be managed with interruption and/or dose
522 reduction of the treatment with Gleevec. (See DOSAGE AND ADMINISTRATION).

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

529 ***Hypereosinophilic cardiac Toxicity:*** In patients with hypereosinophilic syndrome and cardiac
530 involvement, cases of cardiogenic shock/left ventricular dysfunction have been associated
531 with the initiation of imatinib therapy. The condition was reported to be reversible with the
532 administration of systemic steroids, circulatory support measures and temporarily withholding
533 imatinib. Myelodysplastic/ myeloproliferative disease and systemic mastocytosis may be
534 associated with high eosinophil levels. Performance of an echocardiogram and determination
535 of serum troponin should therefore be considered in patients with HES/CEL, and in patients
536 with MDS/MPD or ASM associated with high eosinophil levels. If either is abnormal, the
537 prophylactic use of systemic steroids (1-2 mg/kg) for one to two weeks concomitantly with
538 imatinib should be considered at the initiation of therapy.

539 **Severe congestive heart failure and left ventricular dysfunction:** Severe congestive heart
540 failure and left ventricular dysfunction have occasionally been reported in patients taking
541 Gleevec. Most of the patients with reported cardiac events have had other co-morbidities and
542 risk factors, including advanced age and previous medical history of cardiac disease. In an
543 international randomized phase 3 study in 1,106 patients with newly diagnosed Ph+ CML in
544 chronic phase, severe cardiac failure and left ventricular dysfunction were observed in 0.7%
545 of patients taking Gleevec compared to 0.9% of patients taking IFN + Ara-C. Patients with
546 cardiac disease or risk factors for cardiac failure should be monitored carefully and any
547 patient with signs or symptoms consistent with cardiac failure should be evaluated and
548 treated.

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

559 Drug Interactions

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

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

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

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

568 Substances that are inducers of CYP3A4 activity may increase metabolism and decrease
569 imatinib plasma concentrations. Co-medications that induce CYP3A4 (e.g., dexamethasone,
570 phenytoin, carbamazepine, rifampin, phenobarbital or St. John's Wort) may significantly
571 reduce exposure to Gleevec. Pretreatment of healthy volunteers with multiple doses of
572 rifampin followed by a single dose of Gleevec, increased Gleevec oral-dose clearance by
573 3.8-fold, which significantly ($p < 0.05$) decreased mean C_{max} and $AUC_{(0-\infty)}$. In patients where
574 rifampin or other CYP3A4 inducers are indicated, alternative therapeutic agents with less
575 enzyme induction potential should be considered. (See CLINICAL PHARMACOLOGY and
576 DOSAGE AND ADMINISTRATION.)

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

578 Gleevec increases the mean C_{max} and AUC of simvastatin (CYP3A4 substrate) 2- and
579 3.5-fold, respectively, suggesting an inhibition of the CYP3A4 by Gleevec. Particular caution
580 is recommended when administering Gleevec with CYP3A4 substrates that have a narrow
581 therapeutic window (e.g., cyclosporine or pimozone). Gleevec will increase plasma
582 concentration of other CYP3A4 metabolized drugs (e.g., triazolo-benzodiazepines,
583 dihydropyridine calcium channel blockers, certain HMG-CoA reductase inhibitors, etc.).

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

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

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

594 **Carcinogenesis, Mutagenesis, Impairment of Fertility**

595 The urogenital tract from a 2-year carcinogenicity study in rats receiving doses of 15, 30 and
596 60 mg/kg/day of imatinib mesylate showed renal adenomas/carcinomas, urinary bladder
597 papillomas and papillomas/carcinomas of the preputial and clitoral gland. Evaluation of other
598 organs in the rats is ongoing.

599 The papilloma/carcinoma of the preputial/clitoral gland were noted at 30 and
600 60 mg/kg/day (approximately 0.5 to 4 times the human daily exposure at 400 mg/day). The
601 kidney adenoma/carcinoma and the urinary bladder papilloma were noted at 60 mg/kg/day.
602 No tumors in the urogenital tract were observed at 15 mg/kg/day.

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

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

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

619 **Pregnancy**

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

621 **Nursing Mothers**

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

631 **Pediatric Use**

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

637 **Geriatric Use**

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

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

648 **ADVERSE REACTIONS**649 **Chronic Myeloid Leukemia**

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

654 The most frequently reported drug-related adverse events were edema, nausea and
 655 vomiting, muscle cramps, musculoskeletal pain, diarrhea and rash (Table 10 for newly
 656 diagnosed CML, Table 11 for other CML patients). Edema was most frequently periorbital or
 657 in lower limbs and was managed with diuretics, other supportive measures, or by reducing the
 658 dose of Gleevec[®] (imatinib mesylate). (See DOSAGE AND ADMINISTRATION.) The
 659 frequency of severe superficial edema was 1.1%-6%.

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

668 Adverse events, regardless of relationship to study drug, that were reported in at least
 669 10% of the patients treated in the Gleevec studies are shown in Tables 10 and 11.

670

671 **Table 10 Adverse Experiences Reported in Newly Diagnosed CML Clinical Trial**
 672 **(≥10% of all patients)⁽¹⁾**

Preferred Term	All Grades		CTC Grades 3/4	
	Gleevec [®] N=551 (%)	IFN+Ara-C N=533 (%)	Gleevec [®] N=551 (%)	IFN+Ara-C N=533 (%)
Fluid Retention	59.2	10.7	1.8	0.9
– Superficial Edema	57.5	9.2	1.1	0.4
– Other Fluid Retention Events	6.9	1.9	0.7	0.6
Nausea	47	61.5	0.9	5.1
Muscle Cramps	43.2	11.4	1.6	0.2
Musculoskeletal Pain	39.2	44.1	3.4	8.1
Diarrhea	38.5	42	2.0	3.2
Rash and Related Terms	37.2	25.7	2.4	2.4

Fatigue	37.0	66.8	1.6	25.0
Headache	33.6	43.3	0.5	3.6
Joint Pain	30.3	39.4	2.5	7.3
Abdominal Pain	29.9	25.0	2.5	3.9
Nasopharyngitis	26.9	8.4	0	0.2
Hemorrhage	24.1	20.8	1.1	1.5
- GI Hemorrhage	1.3	1.1	0.5	0.2
- CNS Hemorrhage	0.2	0.2	0	0.2
Myalgia	22.5	38.8	1.5	8.1
Vomiting	20.5	27.4	1.5	3.4
Dyspepsia	17.8	9.2	0	0.8
Cough	17.4	23.1	0.2	0.6
Pharyngolaryngeal Pain	16.9	11.3	0.2	0
Upper Respiratory Tract Infection	16.5	8.4	0.2	0.4
Dizziness	15.8	24.2	0.9	3.6
Pyrexia	15.4	42.4	0.9	3.0
Weight Increased	15.2	2.1	1.6	0.4
Insomnia	13.2	18.8	0	2.3
Depression	12.7	35.8	0.5	13.1
Influenza	11.1	6.0	0.2	0.2

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

675 **Table 11 Adverse Experiences Reported in Other CML Clinical Trials ($\geq 10\%$ of all**
676 **patients in any trial)⁽¹⁾**

Preferred Term	Myeloid Blast Crisis (n= 260)		Accelerated Phase (n=235)		Chronic Phase, IFN Failure (n=532)	
	%		%		%	
	All Grades	Grade 3/4	All Grades	Grade 3/4	All Grades	Grade 3/4
Fluid Retention	72	11	76	6	69	4
- Superficial Edema	66	6	74	3	67	2
- Other Fluid Retention Events ⁽²⁾	22	6	15	4	7	2
Nausea	71	5	73	5	63	3
Muscle Cramps	28	1	47	0.4	62	2
Vomiting	54	4	58	3	36	2

Diarrhea	43	4	57	5	48	3
Hemorrhage	53	19	49	11	30	2
- CNS Hemorrhage	9	7	3	3	2	1
- GI Hemorrhage	8	4	6	5	2	0.4
Musculoskeletal Pain	42	9	49	9	38	2
Fatigue	30	4	46	4	48	1
Skin Rash	36	5	47	5	47	3
Pyrexia	41	7	41	8	21	2
Arthralgia	25	5	34	6	40	1
Headache	27	5	32	2	36	0.6
Abdominal Pain	30	6	33	4	32	1
Weight Increased	5	1	17	5	32	7
Cough	14	0.8	27	0.9	20	0
Dyspepsia	12	0	22	0	27	0
Myalgia	9	0	24	2	27	0.2
Nasopharyngitis	10	0	17	0	22	0.2
Asthenia	18	5	21	5	15	0.2
Dyspnea	15	4	21	7	12	0.9
Upper Respiratory Tract Infection	3	0	12	0.4	19	0
Anorexia	14	2	17	2	7	0
Night Sweats	13	0.8	17	1	14	0.2
Constipation	16	2	16	0.9	9	0.4
Dizziness	12	0.4	13	0	16	0.2
Pharyngitis	10	0	12	0	15	0
Insomnia	10	0	14	0	14	0.2
Pruritus	8	1	14	0.9	14	0.8
Hypokalemia	13	4	9	2	6	0.8
Pneumonia	13	7	10	7	4	1
Anxiety	8	0.8	12	0	8	0.4
Liver Toxicity	10	5	12	6	6	3
Rigors	10	0	12	0.4	10	0
Chest Pain	7	2	10	0.4	11	0.8
Influenza	0.8	0.4	6	0	11	0.2
Sinusitis	4	0.4	11	0.4	9	0.4

677
678

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

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

681 **Hematologic Toxicity**

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

685 In patients with newly diagnosed CML, cytopenias were less frequent than in the other
686 CML patients (see Tables 12 and 13). The frequency of grade 3 or 4 neutropenia and
687 thrombocytopenia was between 2- and 3-fold higher in blast crisis and accelerated phase
688 compared to chronic phase (see Tables 12 and 13). The median duration of the neutropenic
689 and thrombocytopenic episodes varied from 2 to 3 weeks, and from 2 to 4 weeks,
690 respectively.

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

694 **Hepatotoxicity**

695 Severe elevation of transaminases or bilirubin occurred in 3%-6% (see Table 12) and were
696 usually managed with dose reduction or interruption (the median duration of these episodes
697 was approximately 1 week). Treatment was discontinued permanently because of liver
698 laboratory abnormalities in less than 0.5% of CML patients. However, one patient, who was
699 taking acetaminophen regularly for fever, died of acute liver failure. In the GIST trial, grade
700 3 or 4 SGPT (ALT) elevations were observed in 6.8% of patients and grade 3 or 4 SGOT
701 (AST) elevations were observed in 4.8% of patients. Bilirubin elevation was observed in
702 2.7% of patients.

703 **Adverse Reactions in Pediatric Population**

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

710 **Adverse Effects in Other Subpopulations**

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

716

Table 12 Lab Abnormalities in Newly Diagnosed CML Trial

CTC Grades	Gleevec® N=551 %		IFN+Ara-C N=533 %	
	Grade 3	Grade 4	Grade 3	Grade 4
Hematology Parameters				
- Neutropenia*	12.3	3.1	20.8	4.3
- Thrombocytopenia*	8.3	0.2	15.9	0.6
- Anemia	3.1	0.9	4.1	0.2
Biochemistry Parameters				
- Elevated Creatinine	0	0	0.4	0
- Elevated Bilirubin	0.7	0.2	0.2	0
- Elevated Alkaline Phosphatase	0.2	0	0.8	0
- Elevated SGOT (AST)	2.9	0.2	3.8	0.4
- Elevated SGPT (ALT)	3.1	0.4	5.6	0

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

718

719

Table 13 Lab Abnormalities in Other CML Clinical Trials

CTC Grades	Myeloid Blast Crisis (n=260) 600 mg n=223 400 mg n=37 %		Accelerated Phase (n=235) 600 mg n=158 400 mg n=77 %		Chronic Phase, IFN Failure (n=532) 400 mg %	
	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	4.6	0	5.5	0.4	0.2	0

Phosphatase						
- 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

720 CTC Grades: neutropenia (Grade 3 $\geq 0.5-1.0 \times 10^9/L$, Grade 4 $< 0.5 \times 10^9/L$), thrombocytopenia (Grade
721 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
722 creatinine (Grade 3 $> 3-6$ x upper limit normal range [ULN], Grade 4 > 6 x ULN), elevated bilirubin
723 (Grade 3 $> 3-10$ x ULN, Grade 4 > 10 x ULN), elevated alkaline phosphatase (Grade 3 $> 5-20$ x ULN,
724 Grade 4 > 20 x ULN), elevated SGOT or SGPT (Grade 3 $> 5-20$ x ULN, Grade 4 > 20 x ULN)

725 Acute Lymphoblastic Leukemia

726 The adverse reactions were similar for Ph+ ALL as for CML. The most frequently reported
727 drug-related adverse events reported in the Ph+ ALL studies were mild nausea, vomiting,
728 diarrhea, myalgia, muscle cramps and rash, which were easily manageable. Superficial
729 edemas were a common finding in all studies and were described primarily as periorbital or
730 lower limb edemas. However, these edemas were rarely severe and may be managed with
731 diuretics, other supportive measures, or in some patients by reducing the dose of Gleevec.

732 Myelodysplastic/Myeloproliferative Diseases

733 Adverse events, regardless of relationship to study drug, that were reported in at least 10% of
734 the patients treated with Gleevec for MDS/MPD in the phase 2 study, are shown in Table 14.
735

736 **Table 14 Adverse Experiences Reported (more than one patient) in MPD Patients**
737 **in the phase 2 study ($\geq 10\%$ all patients) all Grades**

Preferred term	N=7 n (%)
Nausea	4 (57.1)
Diarrhea	3 (42.9)
Anemia	2 (28.6)
Fatigue	2 (28.6)
Muscle cramp	3 (42.9)
Arthralgia	2 (28.6)
Periorbital edema	2 (28.6)

738 Aggressive Systemic Mastocytosis

739 All ASM patients experienced at least one adverse event at some time. The most frequently
740 reported adverse events were diarrhea, nausea, ascites, muscle cramps, dyspnea, fatigue,
741 peripheral edema, anemia, pruritis, rash and lower respiratory tract infection. None of the 5
742 patients in the phase 2 study with ASM discontinued Gleevec due to drug-related adverse
743 events or abnormal laboratory values.

744 **Hypereosinophilic Syndrome and Chronic Eosinophilic Leukemia**

745 The safety profile in the HES/CEL patient population does not appear to be different from the
 746 known safety profile of imatinib observed in other hematologic malignancy populations, such
 747 as CML. All patients experienced at least one adverse event, the most common being
 748 gastrointestinal, cutaneous and musculoskeletal disorders. Hematological abnormalities were
 749 also frequent, with instances of CTC grade 3 leukopenia, neutropenia, lymphopenia and
 750 anemia.

751 **Dermatofibrosarcoma Protuberans**

752 Adverse events, regardless of relationship to study drug, that were reported in at least 10% of
 753 the 12 patients treated with Gleevec for DFSP in the phase 2 study are shown in Table 15.

754 **Table 15 Adverse Experiences Reported in DFSP Patients in the Phase 2 Study**
 755 **(≥10% all patients) all Grades**

Preferred term	N=12 n (%)
Nausea	5 (41.7)
Diarrhea	3 (25.0)
Vomiting	3 (25.0)
Periorbital edema	4 (33.3)
Face edema	2 (16.7)
Rash	3 (25.0)
Fatigue	5 (41.7)
Edema peripheral	4 (33.3)
Pyrexia	2 (16.7)
Eye edema	4 (33.3)
Lacrimation increased	3 (25.0)
Dyspnea exertional	2 (16.7)
Anemia	3 (25.0)
Rhinitis	2 (16.7)
Anorexia	2 (16.7)

756 Clinically relevant or severe laboratory abnormalities in the 12 patients treated with Gleevec
 757 for DFSP in the phase 2 study are presented in Table 16.

758

759

760 **Table 16 Laboratory Abnormalities Reported in DFSP Patients in the Phase 2 Study**

CTC Grades	N=12	
Hematology Parameters	Grade 3	Grade 4

- Anemia	17 %	0 %
- Thrombocytopenia	17 %	0 %
- Neutropenia	0 %	8 %

Biochemistry Parameters

- Elevated Creatinine	0 %	8 %
-----------------------	-----	-----

761 CTC Grades: neutropenia (Grade 3 ≥ 0.5 - $1.0 \times 10^9/L$, Grade 4 $< 0.5 \times 10^9/L$), thrombocytopenia (Grade
762 3 ≥ 10 - $50 \times 10^9/L$, Grade 4 $< 10 \times 10^9/L$), anemia (Grade 3 ≥ 65 - 80 g/L, grade 4 < 65 g/L), elevated
763 creatinine (Grade 3 > 3 - 6 x upper limit normal range [ULN], Grade 4 > 6 x ULN),
764

765 Gastrointestinal Stromal Tumors

766 The majority of Gleevec-treated patients experienced adverse events at some time. The most
767 frequently reported adverse events were edema, nausea, diarrhea, abdominal pain, muscle
768 cramps, fatigue, and rash. Most events were of mild-to-moderate severity. Drug was
769 discontinued for adverse events in 7 patients (5%) in both dose levels studied. Superficial
770 edema, most frequently periorbital or lower extremity edema, was managed with diuretics,
771 other supportive measures, or by reducing the dose of Gleevec[®] (imatinib mesylate).
772 (See DOSAGE AND ADMINISTRATION.) Severe (CTC Grade 3/4) superficial edema was
773 observed in 3 patients (2%), including face edema in one patient. Grade 3/4 pleural effusion
774 or ascites was observed in 3 patients (2%).

775 Adverse events, regardless of relationship to study drug, that were reported in at least
776 10% of the patients treated with Gleevec are shown in Table 17. No major differences were
777 seen in the severity of adverse events between the 400-mg or 600-mg treatment groups,
778 although overall incidence of diarrhea, muscle cramps, headache, dermatitis, and edema was
779 somewhat higher in the 600-mg treatment group.

780

781 **Table 17 Adverse Experiences Reported in GIST Trial ($\geq 10\%$ of all patients at**
782 **either dose)⁽¹⁾**

	All CTC Grades		CTC Grade 3/4	
	Initial dose (mg/day)		Initial dose (mg/day)	
	400 mg (n=73)	600 mg (n=74)	400 mg (n=73)	600 mg (n=74)
Preferred Term	%	%	%	%
Fluid Retention	81	80	7	12
- Superficial Edema	81	77	6	5
- Pleural Effusion or Ascites	15	12	3	8
Diarrhea	59	70	3	7

Nausea	63	74	6	4
Fatigue	48	53	1	1
Muscle Cramps	47	58	0	0
Abdominal Pain	40	37	11	4
Rash and Related Terms	38	53	4	3
Vomiting	38	35	3	5
Musculoskeletal Pain	37	30	6	1
Headache	33	39	0	0
Flatulence	30	34	0	0
Any Hemorrhage	26	34	6	11
- Tumor Hemorrhage	1	4	1	4
- Cerebral Hemorrhage	1	0	1	0
- GI Tract Hemorrhage	4	4	4	3
- Other Hemorrhage ⁽²⁾	22	27	0	5
Pyrexia	25	16	3	0
Back Pain	23	26	6	0
Nasopharyngitis	21	27	0	0
Insomnia	19	18	1	0
Lacrimation Increased	16	18	0	0
Dyspepsia	15	15	0	0
Upper Respiratory Tract Infection	14	18	0	0
Liver Toxicity	12	12	6	8
Dizziness	12	11	0	0
Loose Stools	12	10	0	0
Operation	12	8	6	4
Pharyngolaryngeal Pain	12	7	0	0
Joint Pain	11	15	1	0
Constipation	11	10	0	1
Anxiety	11	7	0	0
Taste Disturbance	3	15	0	0
⁽¹⁾ All adverse events occurring in $\geq 10\%$ of patients are listed regardless of suspected relationship to treatment.				
⁽²⁾ This category includes conjunctival hemorrhage, blood in stool, epistaxis, hematuria, post-procedural hemorrhage, bruising, and contusion.				

784 Clinically relevant or severe abnormalities of routine hematologic or biochemistry
785 laboratory values are presented in Table 18.

786 **Table 18 Laboratory Abnormalities in GIST Trial**

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

787 CTC Grades: neutropenia (Grade 3 ≥ 0.5 - $1.0 \times 10^9/L$, Grade 4 $< 0.5 \times 10^9/L$), thrombocytopenia (Grade
788 3 ≥ 10 - $50 \times 10^9/L$, Grade 4 $< 10 \times 10^9/L$), anemia (Grade 3 ≥ 65 - 80 g/L, grade 4 < 65 g/L), elevated
789 creatinine (Grade 3 > 3 - $6 \times$ upper limit normal range [ULN], Grade 4 $> 6 \times$ ULN), elevated bilirubin
790 (Grade 3 > 3 - $10 \times$ ULN, Grade 4 $> 10 \times$ ULN), elevated alkaline phosphatase, SGOT or SGPT (Grade 3
791 > 5 - $20 \times$ ULN, Grade 4 $> 20 \times$ ULN), albumin (Grade 3 < 20 g/L)
792

793 **Additional Data From Multiple Clinical Trials**

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

797 **Cardiovascular:** *Infrequent:* cardiac failure, tachycardia, hypertension, hypotension, flushing,
798 peripheral coldness

799 *Rare:* pericarditis

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

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

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

- 804 *Rare*: vesicular rash, Stevens-Johnson syndrome, acute generalized exanthematous pustulosis,
805 acute febrile neutrophilic dermatosis (Sweet's syndrome)
- 806 ***Digestive: Less common***: abdominal distention, gastroesophageal reflux, mouth ulceration
807 *Infrequent*: gastric ulcer, gastroenteritis, gastritis
- 808 *Rare*: colitis, ileus/intestinal obstruction, pancreatitis, diverticulitis, tumor hemorrhage/tumor
809 necrosis, gastrointestinal perforation (see PRECAUTIONS)
- 810 ***General Disorders and Administration Site Conditions: Rare***: tumor necrosis
- 811 ***Hematologic: Infrequent***: pancytopenia
- 812 *Rare*: aplastic anemia
- 813 ***Hepatobiliary: Uncommon***: hepatitis
- 814 *rare*: hepatic failure
- 815 ***Hypersensitivity: Rare***: angioedema
- 816 ***Infections: Infrequent***: sepsis, herpes simplex, herpes zoster
- 817 ***Metabolic and Nutritional: Infrequent***: hypophosphatemia, dehydration, gout, appetite
818 disturbances, weight decreased
- 819 *Rare*: hyperkalemia, hyponatremia
- 820 ***Musculoskeletal: Less common***: joint swelling
- 821 *Infrequent*: sciatica, joint and muscle stiffness
- 822 *Rare*: avascular necrosis/hip osteonecrosis
- 823 ***Nervous System/Psychiatric: Less common***: paresthesia
- 824 *Infrequent*: depression, anxiety, syncope, peripheral neuropathy, somnolence, migraine,
825 memory impairment
- 826 *Rare*: increased intracranial pressure, cerebral edema (including fatalities), confusion,
827 convulsions
- 828 ***Renal: Infrequent***: renal failure, urinary frequency, hematuria
- 829 ***Reproductive: Infrequent***: breast enlargement, menorrhagia, sexual dysfunction
- 830 ***Respiratory: Rare***: interstitial pneumonitis, pulmonary fibrosis
- 831 ***Special Senses: Less common***: conjunctivitis, vision blurred
- 832 *Infrequent*: conjunctival hemorrhage, dry eye, vertigo, tinnitus
- 833 *Rare*: macular edema, papilledema, retinal hemorrhage, glaucoma, vitreous hemorrhage
- 834 ***Vascular Disorders: Rare***: thrombosis/embolism

835 **OVERDOSAGE**

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

839 A patient with myeloid blast crisis experienced Grade 1 elevations of serum creatinine,
840 Grade 2 ascites and elevated liver transaminase levels, and Grade 3 elevations of bilirubin
841 after inadvertently taking 1,200 mg of Gleevec daily for 6 days. Therapy was temporarily
842 interrupted and complete reversal of all abnormalities occurred within 1 week. Treatment was
843 resumed at a dose of 400 mg daily without recurrence of adverse events. Another patient
844 developed severe muscle cramps after taking 1,600 mg of Gleevec daily for 6 days. Complete
845 resolution of muscle cramps occurred following interruption of therapy and treatment was
846 subsequently resumed. Another patient that was prescribed 400 mg daily, took 800 mg of
847 Gleevec on Day 1 and 1,200 mg on Day 2. Therapy was interrupted, no adverse events
848 occurred and the patient resumed therapy.

849 **DOSAGE AND ADMINISTRATION**

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

852 **Philadelphia chromosome positive chronic myeloid leukemia (Ph+ CML)**

853 The recommended dosage of Gleevec[®] (imatinib mesylate) is 400 mg/day for adult
854 patients in chronic phase CML and 600 mg/day for adult patients in accelerated phase or blast
855 crisis. The recommended dosage of Gleevec for children with newly diagnosed Ph+ CML is
856 340 mg/m²/day (not to exceed 600 mg). The recommended Gleevec dosage is 260 mg/m²/day
857 for children with Ph+ chronic phase CML recurrent after stem cell transplant or who are
858 resistant to interferon-alpha therapy.

859 **Philadelphia chromosome positive acute lymphoblastic leukemia (Ph+ALL)**

860 The recommended dose of Gleevec is 600 mg/day for adult patients with
861 relapsed/refractory Ph+ ALL.

862 **Myelodysplastic/Myeloproliferative diseases (MDS/MPD)**

863 The recommended dosage of Gleevec is 400 mg/day for adult patients with
864 MDS/MPD.

865 **Aggressive systemic mastocytosis (ASM)**

866 The recommended dose of Gleevec is 400 mg/day for adult patients with ASM without
867 the D816V c-Kit mutation. If c-Kit mutational status is not known or unavailable, treatment
868 with Gleevec 400 mg/day may be considered for patients with ASM not responding
869 satisfactorily to other therapies. For patients with ASM associated with eosinophilia, a clonal
870 hematological disease related to the fusion kinase FIP1L1-PDGFR α , a starting dose of 100
871 mg/day is recommended. Dose increase from 100 mg to 400 mg for these patients may be

872 considered in the absence of adverse drug reactions if assessments demonstrate an insufficient
873 response to therapy.

874 **Hypereosinophilic syndrome/chronic eosinophilic leukemia (HES/CEL)**

875 For adult patients with HES/CEL the recommended dose of Gleevec is 400 mg/day.
876 HES/CEL patients with demonstrated FIP1L1-PDGFR α fusion kinase, a starting dose of
877 100 mg/day is recommended. Dose increase from 100 mg to 400 mg for these patients may be
878 considered in the absence of adverse drug reactions if assessments demonstrate an insufficient
879 response to therapy.

880 **Dermatofibrosarcoma protuberans (DFSP)**

881 The recommended dose of Gleevec is 800 mg/day for adult patients with DFSP.

882 **Gastrointestinal stromal tumors (GIST)**

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

885 **General Information**

886 The prescribed dose should be administered orally, with a meal and a large glass of
887 water. Doses of 400 mg or 600 mg should be administered once daily, whereas a dose of
888 800 mg should be administered as 400 mg twice a day.

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

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

895 For patients unable to swallow the film-coated tablets, the tablets may be dispersed in
896 a glass of water or apple juice. The required number of tablets should be placed in the
897 appropriate volume of beverage (approximately 50 mL for a 100-mg tablet, and 200 mL for a
898 400-mg tablet) and stirred with a spoon. The suspension should be administered immediately
899 after complete disintegration of the tablet(s).

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

902 In CML, a dose increase from 400 mg to 600 mg in adult patients with chronic phase
903 disease, or from 600 mg to 800 mg (given as 400 mg twice daily) in adult patients in
904 accelerated phase or blast crisis may be considered in the absence of severe adverse drug
905 reaction and severe non-leukemia related neutropenia or thrombocytopenia in the following
906 circumstances: disease progression (at any time), failure to achieve a satisfactory hematologic
907 response after at least 3 months of treatment, failure to achieve a cytogenetic response after
908 6-12 months of treatment, or loss of a previously achieved hematologic or cytogenetic
909 response.

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

913 For daily dosing of 800 mg and above, dosing should be accomplished using the
 914 400-mg tablet to reduce exposure to iron.

915 **Dose Adjustment for Hepatotoxicity and Other Non-Hematologic Adverse** 916 **Reactions**

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

920 If elevations in bilirubin >3 x institutional upper limit of normal (IULN) or in liver
 921 transaminases >5 x IULN occur, Gleevec should be withheld until bilirubin levels have
 922 returned to a <1.5 x IULN and transaminase levels to <2.5 x IULN. In adults, treatment with
 923 Gleevec may then be continued at a reduced daily dose (i.e., 400 mg to 300 mg, 600 mg to
 924 400 mg or 800 mg to 600 mg). In children, daily doses can be reduced under the same
 925 circumstances from $340 \text{ mg/m}^2/\text{day}$ to $260 \text{ mg/m}^2/\text{day}$ or from $260 \text{ mg/m}^2/\text{day}$ to 200
 926 $\text{mg/m}^2/\text{day}$, respectively.

927 **Dose Adjustment for Hematologic Adverse Reactions**

928 Dose reduction or treatment interruptions for severe neutropenia and thrombocytopenia are
 929 recommended as indicated in Table 19.

930 **Table 19 Dose Adjustments for Neutropenia and Thrombocytopenia**

ASM associated with eosinophilia (starting dose 100 mg)	ANC $< 1.0 \times 10^9/\text{L}$ and/or platelets $< 50 \times 10^9/\text{L}$	1. Stop Gleevec until ANC $\geq 1.5 \times 10^9/\text{L}$ and platelets $\geq 75 \times 10^9/\text{L}$. 2. Resume treatment with Gleevec at previous dose (i.e. before severe adverse reaction).
HES/CEL with FIP1L1-PDGFR α fusion kinase (starting dose 100 mg)	ANC $< 1.0 \times 10^9/\text{L}$ and/or platelets $< 50 \times 10^9/\text{L}$	1. Stop Gleevec until ANC $\geq 1.5 \times 10^9/\text{L}$ and platelets $\geq 75 \times 10^9/\text{L}$. 2. Resume treatment with Gleevec at previous dose (i.e. before severe adverse reaction).
Chronic Phase CML (starting dose 400 mg) MDS/MPD, ASM and HES/CEL (starting dose 400 mg)	ANC $< 1.0 \times 10^9/\text{L}$ and/or Platelets $< 50 \times 10^9/\text{L}$	1. Stop Gleevec until ANC $\geq 1.5 \times 10^9/\text{L}$ and platelets $\geq 75 \times 10^9/\text{L}$ 2. Resume treatment with Gleevec at the original starting dose of 400 mg or 600 mg 3. If recurrence of ANC $< 1.0 \times 10^9/\text{L}$

GIST (starting dose either 400 mg or 600 mg)		and/or platelets $<50 \times 10^9/L$, repeat step 1 and resume Gleevec at a reduced dose (300 mg if starting dose was 400 mg, 400 mg if starting dose was 600 mg)
Ph+ CML : Accelerated Phase and Blast Crisis (starting dose 600 mg) Ph+ ALL (starting dose 600 mg)	ANC $<0.5 \times 10^9/L$ and/or Platelets $<10 \times 10^9/L$	<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 $\geq 1 \times 10^9/L$ and platelets $\geq 20 \times 10^9/L$ and then resume treatment at 300 mg
DFSP (starting dose 800 mg)	ANC $< 1.0 \times 10^9/L$ and/or platelets $< 50 \times 10^9/L$	<ol style="list-style-type: none"> 1. Stop Gleevec until ANC $\geq 1.5 \times 10^9/L$ and platelets $\geq 75 \times 10^9/L$. 2. Resume treatment with Gleevec at 600 mg 3. In the event of recurrence of ANC $< 1.0 \times 10^9/L$ and/or platelets $< 50 \times 10^9/L$, repeat step 1 and resume Gleevec at reduced dose of 400 mg.
Newly diagnosed pediatric chronic phase CML (start at dose 340 mg/m^2)	ANC $< 1.0 \times 10^9/L$ and/or platelets $< 50 \times 10^9/L$	<ol style="list-style-type: none"> 1. Stop Gleevec until ANC $\geq 1.5 \times 10^9/L$ and platelets $\geq 75 \times 10^9/L$. 2. Resume treatment with Gleevec at previous dose (i.e. before severe adverse reaction) 3. In the event of recurrence of ANC $< 1.0 \times 10^9/L$ and/or platelets $< 50 \times 10^9/L$, repeat step 1 and resume Gleevec at reduced dose of 260 mg/m^2
Pediatric patients with chronic phase CML recurring after transplant or resistant to Interferon (start at dose 260 mg/m^2)	ANC $< 1.0 \times 10^9/L$ and/or platelets $< 50 \times 10^9/L$	<ol style="list-style-type: none"> 1. Stop Gleevec until ANC $\geq 1.5 \times 10^9/L$ and platelets $\geq 75 \times 10^9/L$. 2. Resume treatment with Gleevec at previous dose (i.e. before severe adverse reaction) 3. In the event of recurrence of ANC $< 1.0 \times 10^9/L$ and/or platelets $< 50 \times 10^9/L$, repeat step 1 and resume Gleevec at reduced dose of 200 mg/m^2

932 **HOW SUPPLIED**

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

934 **100-mg Tablets**

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

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

938 **400-mg Tablets**

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

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

943 **Storage**

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

946 Dispense in a tight container, USP.

947 T2006-XX-XX

948 REV: 2006 XXXXXXXX 2006

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953 Manufactured by:
954 Novartis Pharma Stein AG
955 Stein, Switzerland

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Novartis Pharmaceuticals Corporation
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