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Gleevec™ (imatinib mesylate)

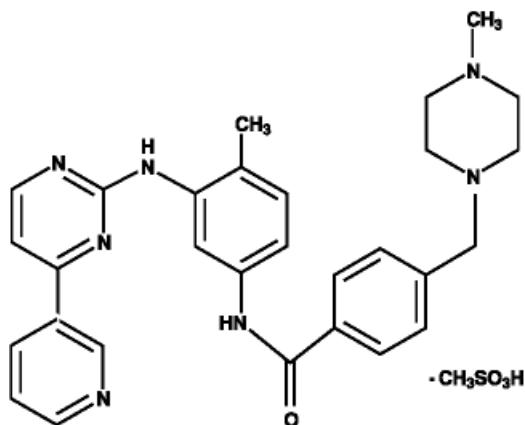
Tablets

Rx only

Prescribing Information

DESCRIPTION

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



15 Imatinib mesylate is a white to off-white to brownish or yellowish tinged crystalline
16 powder. Its molecular formula is C₂₉H₃₁N₇O • CH₄SO₃ and its molecular weight is 589.7.
17 Imatinib mesylate is soluble in aqueous buffers ≤ pH 5.5 but is very slightly soluble to
18 insoluble in neutral/alkaline aqueous buffers. In non-aqueous solvents, the drug substance is
19 freely soluble to very slightly soluble in dimethyl sulfoxide, methanol and ethanol, but is
20 insoluble in n-octanol, acetone and acetonitrile.

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

25 CLINICAL PHARMACOLOGY

26 Mechanism of Action

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

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

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

40 Pharmacokinetics

41 The pharmacokinetics of Gleevec™ (imatinib mesylate) have been evaluated in studies in
42 healthy subjects and in population pharmacokinetic studies in over 900 patients. Imatinib is
43 well absorbed after oral administration with C_{max} achieved within 2-4 hours post-dose. Mean
44 absolute bioavailability is 98%. Following oral administration in healthy volunteers, the
45 elimination half-lives of imatinib and its major active metabolite, the N-desmethyl derivative,
46 were approximately 18 and 40 hours, respectively. Mean imatinib AUC increased
47 proportionally with increasing dose in the range 25 mg-1000 mg. There was 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 ^{14}C -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 14
67 L/h. However, the inter-patient variability of 40% in clearance does not warrant initial dose
68 adjustment based on body weight and/or age but indicates the need for close monitoring for
69 treatment related toxicity.

70 **Special Populations**

71 **Pediatric:** There are no pharmacokinetic data in pediatric patients.

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

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

78 **Drug-Drug Interactions**

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

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

86 **CYP3A4 Inducers:** Pretreatment of 14 healthy volunteers with multiple doses of rifampin,
87 600 mg daily for 8 days, followed by a single 400 mg dose of Gleevec, increased Gleevec
88 oral-dose clearance by 3.8-fold (90% confidence interval = 3.5- to 4.3-fold), which represents
89 mean decreases in C_{max} , $AUC_{(0-24)}$ and $AUC_{(0-\infty)}$ by 54%, 68% and 74%, of the respective
90 values without rifampin treatment. (See PRECAUTIONS and DOSAGE AND
91 ADMINISTRATION)

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

96 **CLINICAL STUDIES**

97 **Chronic Myeloid Leukemia**

98 **Chronic Phase, Newly Diagnosed**

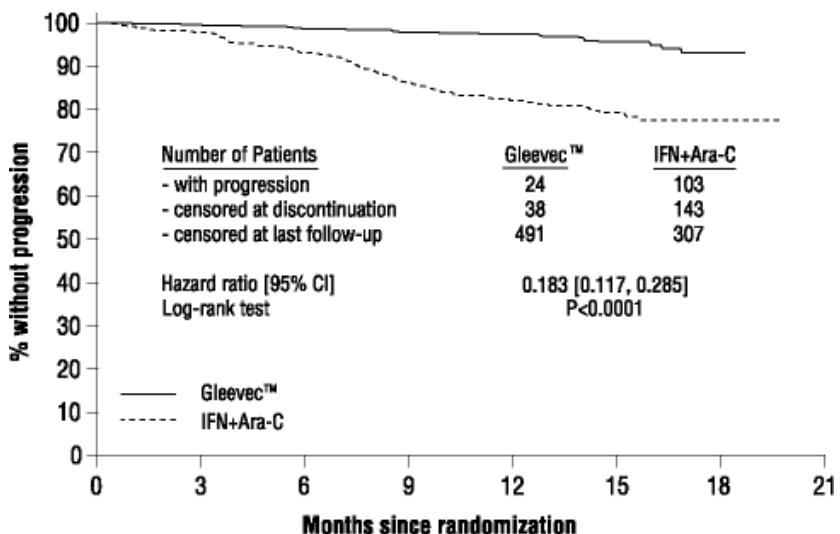
99 An open-label, multicenter, international randomized Phase 3 study has been conducted in
100 patients with newly diagnosed Philadelphia chromosome positive (Ph+) chronic myeloid
101 leukemia (CML) in chronic phase. This study compared treatment with either single-agent

102 Gleevec™ (imatinib mesylate) or a combination of interferon-alfa (IFN) plus cytarabine
103 (Ara-C). Patients were allowed to crossover to the alternative treatment arm if they failed to
104 show a complete hematologic response (CHR) at 6 months, a major cytogenetic response
105 (MCyR) at 12 months, or if they lost a CHR or MCyR. Patients with increasing WBC or
106 severe intolerance to treatment were also allowed to crossover to the alternative treatment arm
107 with the permission of the study monitoring committee (SMC). In the Gleevec arm, patients
108 were treated initially with 400 mg daily. In the IFN arm, patients were treated with a target
109 dose of IFN of 5 MIU/m²/day subcutaneously in combination with subcutaneous Ara-C 20
110 mg/m²/day for 10 days/month.

111 A total of 1106 patients were randomized from 177 centers in 16 countries, 553 to
112 each arm. Baseline characteristics were well balanced between the two arms. Median age was
113 51 years (range 18-70 years), with 21.9% of patients ≥60 years of age. There were 59% males
114 and 41% females; 89.9% Caucasian and 4.7% Black patients. With a median follow-up of 14
115 and 13 months for Gleevec and IFN, respectively, 90% of patients randomized to Gleevec
116 were still receiving first-line treatment. Due to discontinuations and crossovers, only 30% of
117 patients randomized to IFN were still on first-line treatment. In the IFN arm, withdrawal of
118 consent (13.4%) was the most frequent reason for discontinuation of first-line therapy, and the
119 most frequent reason for crossover to the Gleevec arm was severe intolerance to treatment
120 (22.7%).

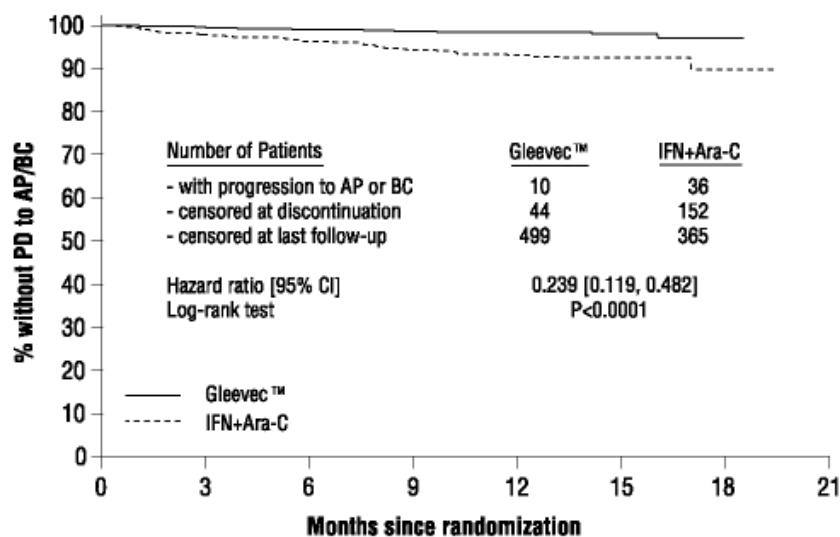
121 The primary efficacy endpoint of the study was progression-free survival (PFS). The
122 final analysis of progression-free survival was planned after 5 years, however, the reported
123 analysis was conducted at one year after the last patient was randomized to the study.
124 Progression was defined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

Figure 1
Time to Progression (ITT Principle)



138

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



139

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

145 **Table 1 Response in Newly Diagnosed CML Study (first-line)**

146 147 (Best Response Rates)	148 Gleevec™ n=553	149 IFN+Ara-C n=553
Hematologic Response¹		
150 CHR rate n (%) [95% CI]	522 (94.4%)* [92.1%, 96.2%]	302 (54.6%)* [50.4%, 58.8%]
Cytogenetic Response²		
152 Major Cytogenetic Response n (%) [95% CI]	419 (75.8%)* [72.0%, 79.3%]	67 (12.1%)* [9.5%, 15.1%]
154 Unconfirmed ³	82.6%*	20.3%*
155 Complete Cytogenetic Response n (%) Unconfirmed ³	297 (53.7%)* 67.8%*	15 (2.7%)* 7.4%*

157 * p<0.001, Fischer's exact test

158 **1 Hematologic response criteria (all responses to be confirmed after ≥4 weeks):**159 WBC<10 x 10⁹/L, platelet <450 x 10⁹/L, myelocyte + metamyelocyte <5% in blood, no blasts and
160 promyelocytes in blood, basophils <20%, no extramedullary involvement.161 **2 Cytogenetic response criteria (confirmed after ≥4 weeks):** complete (0% Ph+ metaphases) or
162 partial (1%-35%). A major response (0%-35%) combines both complete and partial responses.163 **3** Unconfirmed cytogenetic response is based on a single bone marrow cytogenetic evaluation,
164 therefore unconfirmed complete or partial cytogenetic responses might have had a lesser
165 cytogenetic response on a subsequent bone marrow evaluation.

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

173 Late Chronic Phase CML and Advanced Stage CML

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

179 Chronic Phase, Prior Interferon-Treatment

180 532 patients were treated at a starting dose of 400 mg; dose escalation to 600 mg was allowed.
 181 The patients were distributed in three main categories according to their response to prior
 182 interferon: failure to achieve (within 6 months), or loss of a complete hematologic response
 183 (29%), failure to achieve (within 1 year) or loss of a major cytogenetic response (35%), or
 184 intolerance to interferon (36%). Patients had received a median of 14 months of prior IFN
 185 therapy at doses ≥25 x 10⁶ IU/week and were all in late chronic phase, with a median time
 186 from diagnosis of 32 months. Effectiveness was evaluated on the basis of the rate of
 187 hematologic response and by bone marrow exams to assess the rate of major cytogenetic
 188 response (up to 35% Ph+ metaphases) or complete cytogenetic response (0% Ph+

189 metaphases). Efficacy results are reported in Table 2. Results were similar in the three
190 subgroups described above.

191 **Accelerated Phase**

192 235 patients with accelerated phase disease were enrolled. These patients met one or more of
193 the following criteria: $\geq 15\%-<30\%$ blasts in PB or BM; $\geq 30\%$ blasts + promyelocytes in PB
194 or BM; $\geq 20\%$ basophils in PB; and $<100 \times 10^9/L$ platelets. The first 77 patients were started at
195 400 mg, with the remaining 158 patients starting at 600 mg.

196 Effectiveness was evaluated primarily on the basis of the rate of hematologic response,
197 reported as either complete hematologic response, no evidence of leukemia (i.e., clearance of
198 blasts from the marrow and the blood, but without a full peripheral blood recovery as for
199 complete responses), or return to chronic phase CML. Cytogenetic responses were also
200 evaluated. Efficacy results are reported in Table 2. Response rates in accelerated phase CML
201 were higher for the 600 mg dose group than for the 400 mg group: hematologic response
202 (73% vs. 62%), confirmed and unconfirmed major cytogenetic response (28% vs. 18%).

203 **Myeloid Blast Crisis**

204 260 patients with myeloid blast crisis were enrolled. These patients had $\geq 30\%$ blasts in PB or
205 BM and/or extramedullary involvement other than spleen or liver; 95 (37%) had received
206 prior chemotherapy for treatment of either accelerated phase or blast crisis (“pretreated
207 patients”) whereas 165 (63%) had not (“untreated patients”). The first 37 patients were started
208 at 400 mg; the remaining 223 patients were started at 600 mg.

209 Effectiveness was evaluated primarily on the basis of rate of hematologic response,
210 reported as either complete hematologic response, no evidence of leukemia, or return to
211 chronic phase CML using the same criteria as for the study in accelerated phase. Cytogenetic
212 responses were also assessed. Efficacy results are reported in Table 2. The hematologic
213 response rate was higher in untreated patients than in treated patients (36% vs. 22%,
214 respectively) and in the group receiving an initial dose of 600 mg rather than 400 mg (33% vs.
215 16%). The confirmed and unconfirmed major cytogenetic response rate was also higher for
216 the 600 mg dose group than for the 400 mg group (17% vs. 8%).

217 **Table 2 Response in CML Studies**

	Chronic Phase IFN Failure (n=532)	Accelerated Phase (n=235)	Myeloid Blast Crisis (n=260)
		600 mg n=158 400 mg n=77	600 mg n=223 400 mg n=37
			% of patients [CI _{95%}]
Hematologic Response¹	93% [91.0-95.4]	69%[63.0-75.2]	31% [25.2-36.8]
Complete hematologic response (CHR)	93%	37%	7%
No evidence of leukemia (NEL)	Not applicable	12%	5%
Return to chronic phase (RTC)	Not applicable	20%	19%
Major Cytogenetic Response²	53% [48.7-57.3] (unconfirmed ³)	19% [14.3-24.8] (25%)	7% [4.2-10.7] (15%)
Complete ⁴ (unconfirmed ³)	32% (41%)	13% (17%)	1.5% (7%)

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

234 CHR: Chronic phase study [WBC <10 x 10⁹/L, platelet <450 x 10⁹/L, myelocytes + metamyelocytes
 235 <5% in blood, no blasts and promyelocytes in blood, basophils <20%, no extramedullary
 236 involvement] and in the accelerated and blast crisis studies [ANC ≥1.5 x 10⁹/L, platelets ≥100 x
 237 10⁹/L, no blood blasts, BM blasts <5% and no extramedullary disease]

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

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

242 BM=bone marrow, PB=peripheral blood

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

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

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

250 The median time to hematologic response was 1 month. Response duration cannot be
 251 precisely defined because follow-up on most patients is relatively short. In blast crisis, the
 252 estimated median duration of hematologic response is about 10 months. In accelerated phase,
 253 median duration of hematologic response is greater than 12 months but cannot yet be
 254 estimated. Follow-up is insufficient to estimate duration of cytogenetic response in all studies.

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

258

259 **Gastrointestinal Stromal Tumors**

260 One open-label, multinational study was conducted in patients with unresectable or metastatic
 261 malignant gastrointestinal stromal tumors (GIST). In this study 147 patients were enrolled and

262 randomized to receive either 400 mg or 600 mg orally q.d. for up to 24 months. The study was
 263 not powered to show a statistically significant difference in response rates between the two
 264 dose groups. Patients ranged in age from 18 to 83 years old and had a pathologic diagnosis of
 265 Kit-positive unresectable and/or metastatic malignant GIST. Immunohistochemistry was
 266 routinely performed with Kit antibody (A-4502, rabbit polyclonal antiserum, 1:100; DAKO
 267 Corporation, Carpinteria, CA) according to analysis by an avidin-biotin-peroxidase complex
 268 method after antigen retrieval.

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

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

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

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

283 INDICATIONS AND USAGE

284 Gleevec™ (imatinib mesylate) is indicated for the treatment of newly diagnosed adult patients
 285 with Philadelphia chromosome positive chronic myeloid leukemia (CML) in chronic phase.
 286 Follow-up is limited.

287 Gleevec is also indicated for the treatment of patients with Philadelphia chromosome positive
 288 chronic myeloid leukemia (CML) in blast crisis, accelerated phase, or in chronic phase after
 289 failure of interferon-alpha therapy. There are no controlled trials demonstrating a clinical
 290 benefit, such as improvement in disease-related symptoms or increased survival in patients
 291 with CML blast crisis, accelerated phase or chronic phase after failure of alpha interferon.

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

298 CONTRAINDICATIONS

299 Use of Gleevec™ (imatinib mesylate) is contraindicated in patients with hypersensitivity to
 300 imatinib or to any other component of Gleevec.

301 **WARNINGS**

302 **Pregnancy**

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

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

313 Male and female rats were exposed *in utero* to a maternal imatinib mesylate dose of
314 45 mg/kg (approximately one-half the maximum human dose of 800 mg) from day 6 of
315 gestation and through milk during the lactation period. These animals then received no
316 imatinib exposure for nearly 2 months. Body weights were reduced from birth until terminal
317 sacrifice in these rats. Although fertility was not affected, fetal loss was seen when these male
318 and female animals were then mated.

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

322 **PRECAUTIONS**

323 **General**

324 **Fluid Retention and Edema:** Gleevec™ (imatinib mesylate) is often associated with edema
325 and occasionally serious fluid retention (see ADVERSE REACTIONS). Patients should be
326 weighed and monitored regularly for signs and symptoms of fluid retention. An unexpected
327 rapid weight gain should be carefully investigated and appropriate treatment provided. The
328 probability of edema was increased with higher Gleevec dose and age >65 years in the CML
329 studies. Severe superficial edema was reported in 0.9% of newly diagnosed CML patients
330 taking Gleevec, and in 2%-5% of other adult CML patients taking Gleevec. In addition,
331 severe fluid retention (e.g., pleural effusion, pericardial effusion, pulmonary edema, and
332 ascites) was reported in 2%-8% of other adult CML patients taking Gleevec. There have been
333 post-marketing reports, including fatalities, of cerebral edema, increased intracranial pressure,
334 and papilledema in patients with CML treated with Gleevec.

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

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

339 **Hemorrhage:** In the newly diagnosed CML trial, 0.7% of patients had grade 3/4 hemorrhage.
340 In the GIST clinical trial seven patients (5%), four in the 600 mg dose group and three in the
341 400 mg dose group, had a total of eight events of CTC grade 3/4 - gastrointestinal (GI) bleeds
342 (3 patients), intra-tumoral bleeds (3 patients) or both (1 patient). Gastrointestinal tumor sites
343 may have been the source of GI bleeds.

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

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

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

368 Drug Interactions

369 Drugs that may alter imatinib plasma concentrations

370 Drugs that may increase imatinib plasma concentrations:

371 Caution is recommended when administering Gleevec with inhibitors of the CYP3A4 family
372 (e.g., ketoconazole, itraconazole, erythromycin, clarithromycin). Substances that inhibit the
373 cytochrome P450 isoenzyme (CYP3A4) activity may decrease metabolism and increase
374 imatinib concentrations. There is a significant increase in exposure to imatinib when Gleevec
375 is co-administered with ketoconazole (CYP3A4 inhibitor).

376 Drugs that may decrease imatinib plasma concentrations:

377 Substances that are inducers of CYP3A4 activity may increase metabolism and decrease
378 imatinib plasma concentrations. Co-medications that induce CYP3A4 (e.g., dexamethasone,
379 phenytoin, carbamazepine, rifampin, phenobarbital or St. John's Wort) may significantly

reduce exposure to Gleevec. Pretreatment of healthy volunteers with multiple doses of rifampin followed by a single dose of Gleevec, increased Gleevec oral-dose clearance by 3.8-fold, which significantly ($p<0.05$) decreased mean C_{max} and $AUC_{(0-\infty)}$. In patients where rifampin or other CYP3A4 inducers are indicated, alternative therapeutic agents with less enzyme induction potential should be considered. (See CLINICAL PHARMACOLOGY and DOSAGE AND ADMINISTRATION.)

Drugs that may have their plasma concentration altered by Gleevec

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

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

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

Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenicity studies have not been performed with imatinib mesylate.

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

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

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

417 **Pregnancy**

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

419 **Nursing Mothers**

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

429 **Pediatric Use**

430 The safety and effectiveness of Gleevec in pediatric patients have not been established.

431 **Geriatric Use**

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

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

442 **ADVERSE REACTIONS**

443 **Chronic Myeloid Leukemia**

444 The majority of Gleevec-treated patients experienced adverse events at some time. Most
445 events were of mild to moderate grade, but drug was discontinued for adverse events in 2% of
446 patients in chronic phase, 3% in accelerated phase and 5% in blast crisis.

447 The most frequently reported drug-related adverse events were nausea, vomiting,
448 diarrhea, edema, and muscle cramps (Table 4 for newly diagnosed CML, Table 5 for other
449 CML patients). Edema was most frequently periorbital or in lower limbs and was managed
450 with diuretics, other supportive measures, or by reducing the dose of Gleevec™ (imatinib
451 mesylate). (See DOSAGE AND ADMINISTRATION.) The frequency of severe superficial
452 edema was 0.9%-5%.

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

461 Adverse events, regardless of relationship to study drug, that were reported in at least
 462 10% of the patients treated in the Gleevec studies are shown in Tables 4 and 5.

463 **Table 4 Adverse Experiences Reported in Newly Diagnosed CML Clinical Trial**
 464 (**>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	54.1	10.1	0.9	0.9
- Superficial edema	53.2	8.8	0.9	0.4
- Other fluid retention events	3.4	1.5	0	0.6
Nausea	42.5	60.8	0.4	5.1
Muscle cramps	35.4	9.9	1.1	0.2
Musculoskeletal pain	33.6	40.5	2.7	7.7
Rash	31.9	25.0	2.0	2.1
Fatigue	30.7	64.7	1.1	24.0
Diarrhea	30.3	40.9	1.3	3.2
Headache	28.5	41.8	0.4	3.2
Joint pain	26.7	38.3	2.2	6.8
Abdominal pain	23.4	22.9	2.0	3.6
Myalgia	20.9	38.6	1.5	8.1
Nasopharyngitis	19.2	7.7	0	0.2
Hemorrhage	18.9	19.9	0.7	1.3
Dyspepsia	15.1	9.0	0	0.8
Vomiting	14.7	26.6	0.9	3.4
Pharyngolaryngeal pain	14.2	11.4	0.2	0
Dizziness	13.2	23.1	0.5	3.4
Cough	12.5	21.6	0.2	0.6
Upper respiratory tract infection	12.5	7.9	0.2	0.4
Pyrexia	11.8	38.6	0.5	2.8
Weight increased	11.6	1.5	0.7	0.2
Insomnia	11.4	18.4	0	2.3

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

496 **Table 5 Adverse Experiences Reported in Other CML Clinical Trials (≥10% of all patients**
 497 **in any trial)⁽¹⁾**

502 503 Preferred Term	504 505 506 507 508 509 510 511 512 513 514 515 516 517 518 519 520 521 522 523 524 525 526 527 528 529 530 531 532 533 534 535 536 537 538 539 540 541 542 543 544 545 546		504 505 506 507 508 509 510 511 512 513 514 515 516 517 518 519 520 521 522 523 524 525 526 527 528 529 530 531 532 533 534 535 536 537 538 539 540 541 542 543 544 545 546		504 505 506 507 508 509 510 511 512 513 514 515 516 517 518 519 520 521 522 523 524 525 526 527 528 529 530 531 532 533 534 535 536 537 538 539 540 541 542 543 544 545 546	
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Nausea	70	4	71	5	60	2
Fluid retention	71	12	73	6	66	3
- Superficial edema	67	5	71	4	64	2
- Other fluid retention events(2)	22	8	10	3	7	2
Muscle cramps	27	0.8	42	0.4	55	1
Diarrhea	42	4	55	4	43	2
Vomiting	54	4	56	3	32	1
Hemorrhage	52	19	44	9	22	2
- CNS hemorrhage	7	5	2	0.9	1	1
- Gastrointestinal hemorrhage	8	3	5	3	2	0.4
Musculoskeletal pain	43	9	46	9	35	2
Skin rash	35	5	44	4	42	3
Headache	27	5	30	2	34	0.2
Fatigue	29	3	41	4	40	1
Arthralgia	25	4	31	6	36	1
Dyspepsia	11	0	21	0	24	0
Myalgia	8	0	22	2	25	0.2
Weight increase	5	0.8	14	3	30	5
Pyrexia	41	7	39	8	17	1
Abdominal pain	31	6	33	3	29	0.6
Cough	14	0.8	26	0.9	17	0
Dyspnea	14	4	20	7	9	0.6
Anorexia	14	2	17	2	6	0
Constipation	15	2	15	0.9	6	0.2
Nasopharyngitis	8	0	16	0	18	0.2
Night sweats	12	0.8	14	1	10	0.2
Pruritus	8	1	13	0.9	12	0.8
Epistaxis	13	3	13	0	5	0.2
Hypokalemia	13	4	8	2	5	0.2
Petechiae	10	2	5	0.9	1	0
Pneumonia	12	6	8	6	3	0.8
Weakness	12	3	9	3	7	0.2
Upper respiratory tract infection	3	0	9	0.4	15	0
Dizziness	11	0.4	12	0	13	0.2
Insomnia	10	0	13	0	13	0.2
Sore throat	8	0	11	0	11	0
Ecchymosis	11	0.4	6	0.9	2	0
Rigors	10	0	11	0.4	8	0
Asthenia	5	2	11	2	6	0
Influenza	0.8	0.4	6	0	10	0.2

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

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

551 **Hematologic Toxicity**

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

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

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

563 **Hepatotoxicity**

564 Severe elevation of transaminases or bilirubin occurred in 1%-4% (see Tables 6 and 7) and
 565 were usually managed with dose reduction or interruption (the median duration of these
 566 episodes was approximately one week). Treatment was discontinued permanently because of
 567 liver laboratory abnormalities in less than 0.5% of patients. However, one patient, who was
 568 taking acetaminophen regularly for fever, died of acute liver failure.

569 **Adverse Effects in Other Subpopulations**

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

575 **Table 6 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					
581	- Neutropenia*	11.4	2.2	20.3	4.3
582	- Thrombocytopenia*	6.9	0.2	15.8	0.6
583	- Anemia	2.7	0.4	4.1	0.2
Biochemistry Parameters					
585	- Elevated creatinine	0	0	0.4	0
586	- Elevated bilirubin	0.2	0.5	0.2	0
587	- Elevated alkaline				
588	phosphatase	0.2	0	0.8	0
589	- Elevated SGOT (AST)	2.9	0.2	3.8	0.4
590	- Elevated SGPT (ALT)	3.1	0.4	5.6	0

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

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

593 594 595 596 597 598 599 600 601 602 603 604 605 606 607 608 609 610 611 612 613 614 615 616	Myeloid Blast Crisis (n=260)		Accelerated Phase (n=235)		Chronic Phase, IFN Failure (n=532)	
	600 mg n=223 400 mg n=37 %	600 mg n=158 400 mg n=77 %	600 mg n=158 400 mg n=77 %	600 mg n=158 400 mg n=77 %	600 mg 400 mg %	600 mg 400 mg %
CTC Grades	Grade 3	Grade 4	Grade 3	Grade 4	Grade 3	Grade 4
Hematology Parameters						
- Neutropenia	16	48	23	36	27	8
- Thrombocytopenia	29	33	31	13	19	<1
- Anemia	41	11	34	6	6	1
Biochemistry Parameters						
- Elevated creatinine	1.5	0	1.3	0	0.2	0
- Elevated bilirubin	3.8	0	2.1	0	0.8	0
- Elevated alkaline phosphatase	4.6	0	5.1	0.4	0.2	0
- Elevated SGOT (AST)	1.9	0	3.0	0	2.3	0
- Elevated SGPT (ALT)	2.3	0.4	3.8	0	1.9	0

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

617 Gastrointestinal Stromal Tumors

618 The majority of Gleevec-treated patients experienced adverse events at some time. The most
619 frequently reported adverse events were edema, nausea, diarrhea, abdominal pain, muscle
620 cramps, fatigue, and rash. Most events were of mild to moderate severity. Drug was
621 discontinued for adverse events in 6 patients (8%) in both dose levels studied. Superficial
622 edema, most frequently periorbital or lower extremity edema, was managed with diuretics,
623 other supportive measures, or by reducing the dose of Gleevec™ (imatinib mesylate). (See
624 DOSAGE AND ADMINISTRATION.) Severe (CTC grade 3/4) superficial edema was
625 observed in 3 patients (2%), including face edema in one patient. Grade 3/4 pleural effusion
626 or ascites was observed in 3 patients (2%).

627 Adverse events, regardless of relationship to study drug, that were reported in at least
628 10% of the patients treated with Gleevec are shown in Table 8. No major differences were
629 seen in the severity of adverse events between the 400 mg or 600 mg treatment groups,
630 although overall incidence of diarrhea, muscle cramps, headache, dermatitis, and edema was
631 somewhat higher in the 600 mg treatment group.

632 **Table 8 Adverse Experiences Reported in GIST Trial ($\geq 10\%$ of all patients at either
633 dose)⁽¹⁾**

	All CTC Grades Initial dose (mg/day)	CTC Grade 3/4 Initial dose (mg/day)
--	-----------------------------------------	----------------------------------------

	400 mg (n=73) %	600 mg (n=74) %	400 mg (n=73) %	600 mg (n=74) %
Preferred Term				
Fluid retention	71	76	6	3
- Superficial edema	71	76	4	0
- Pleural effusion or ascites	6	4	1	3
Diarrhea	56	60	1	4
Nausea	53	56	3	3
Fatigue	33	38	1	0
Muscle cramps	30	41	0	0
Abdominal pain	37	37	7	3
Skin Rash	26	38	3	3
Headache	25	35	0	0
Vomiting	22	23	1	3
Musculoskeletal pain	19	11	3	0
Flatulence	16	23	0	0
Any hemorrhage	18	19	5	8
- Tumor hemorrhage	1	4	1	4
- Cerebral hemorrhage	1	0	1	0
- GI tract hemorrhage	6	4	4	1
Nasopharyngitis	12	14	0	0
Pyrexia	12	5	0	0
Insomnia	11	11	0	0
Back pain	11	10	1	0
Lacrimation increased	6	11	0	0
Upper respiratory tract infection	6	11	0	0
Taste disturbance	1	14	0	0

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

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

Table 9 Laboratory Abnormalities in GIST Trial

	400 mg (n=73) %	600 mg (n=74) %	Grade 3	Grade 4
CTC Grades				
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

683 CTC grades: neutropenia (grade 3 $\geq 0.5\text{-}1.0 \times 10^9/\text{L}$, grade 4 $< 0.5 \times 10^9/\text{L}$), thrombocytopenia (grade 3
684 $\geq 10\text{-}50 \times 10^9/\text{L}$, grade 4 $< 10 \times 10^9/\text{L}$), anemia (grade 3 $\geq 65\text{-}80 \text{ g/L}$, grade 4 $< 65 \text{ g/L}$), elevated
685 creatinine (grade 3 $> 3\text{-}6 \times \text{upper limit normal range (ULN)}$, grade 4 $> 6 \times \text{ULN}$), elevated bilirubin (grade
686 3 $> 3\text{-}10 \times \text{ULN}$, grade 4 $> 10 \times \text{ULN}$), elevated alkaline phosphatase, SGOT or SGPT (grade 3 $> 5\text{-}20 \times$
687 ULN, grade 4 $> 20 \times \text{ULN}$), albumin (grade 3 $< 20 \text{ g/L}$)

688 **Post-Marketing Experiences**

689 The following adverse events have been reported in association with post-approval use of
690 Gleevec. Because these reactions are reported voluntarily from a population of uncertain size,
691 it is not always possible to estimate their frequency or to establish a causal relationship to
692 drug exposure.

693 **Neurologic:** Increased intracranial pressure, cerebral edema (including fatalities) and
694 papilledema.

695 **OVERDOSAGE**

696 Experience with doses greater than 800 mg is limited. In the event of overdosage, the patient
697 should be observed and appropriate supportive treatment given. An oral dose of
698 1200 mg/m²/day, approximately 2.5 times the human dose of 800 mg, based on body surface
699 area, was not lethal to rats following 14 days of administration. A dose of 3600 mg/m²/day,
700 approximately 7.5 times the human dose of 800 mg, was lethal to rats after 7-10
701 administrations, due to general deterioration of the animals with secondary degenerative
702 histological changes in many tissues.

703 **DOSAGE AND ADMINISTRATION**

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

706 The prescribed dose should be administered orally, with a meal and a large glass of
707 water. Doses of 400 mg or 600 mg should be administered once daily, whereas a dose of
708 800 mg should be administered as 400 mg twice a day.

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

714

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

717 The recommended dosage of Gleevec™ (imatinib mesylate) is 400 mg/day for adult patients
718 in chronic phase CML and 600 mg/day for patients in accelerated phase or blast crisis.

719

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

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

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

733 **Dose Adjustment for Hepatotoxicity and Other Non-Hematologic Adverse 734 Reactions**

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

738 If elevations in bilirubin $>3 \times$ institutional upper limit of normal (IULN) or in liver
 739 transaminases $>5 \times$ IULN occur, Gleevec should be withheld until bilirubin levels have
 740 returned to a $<1.5 \times$ IULN and transaminase levels to $<2.5 \times$ IULN. Treatment with Gleevec
 741 may then be continued at a reduced daily dose (i.e., 400 mg to 300 mg or 600 mg to 400 mg).

742 **Dose Adjustment for Hematologic Adverse Reactions**

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

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

746 Chronic Phase CML 747 (starting dose 400mg)	748 ANC $<1.0 \times 10^9/L$ 749 and/or 750 Platelets $<50 \times 10^9/L$ 751 or GIST 752 (starting dose either 753 400 mg or 600 mg)	754 1. Stop Gleevec until ANC 755 $\geq 1.5 \times 10^9/L$ and 756 platelets $\geq 75 \times 10^9/L$ 757 2. Resume treatment with 758 Gleevec at the original 759 starting dose of 400 mg 760 or 600 mg 761 3. If recurrence of ANC $<1.0 \times$ 762 $10^9/L$ and/or platelets $<50 \times$ 763 $10^9/L$, repeat step 1 and 764 resume Gleevec at a reduced 765 dose (300 mg if starting 766 dose was 400 mg, 400 mg if 767 starting dose was 600 mg)
760 Accelerated Phase 761 CML and Blast Crisis 762 (starting dose 600 mg)	763 ¹ ANC $<0.5 \times 10^9/L$ 764 and/or 765 Platelets $<10 \times 10^9/L$	766 1. Check if cytopenia is 767 related to leukemia 768 (marrow aspirate or biopsy)

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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 $\text{ANC} \geq 1 \times 10^9/\text{L}$ and platelets $\geq 20 \times 10^9/\text{L}$ and then resume treatment at 300 mg.

¹occurring after at least 1 month of treatment

775 HOW SUPPLIED

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

777 100 mg Tablets

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

780 Bottles of 100 tablets NDC 0078-0401-05

781 400 mg Tablets

782

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

785 Bottles of 30 tablets NDC 0078-0402-15

786

787 Storage

788 Store at 25°C (77°F); excursions permitted to 15°C-30°C (59°F-86°F). [See USP Controlled
789 Room Temperature]

790 Protect from moisture

791 Dispense in a tight container USP

792

793

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89019001

796

797

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