

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

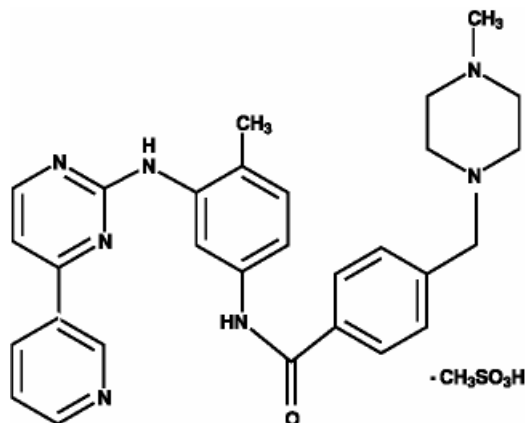
5 **Tablets**

6 **Rx only**

7 **Prescribing Information**

8 **DESCRIPTION**

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



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

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

24 CLINICAL PHARMACOLOGY

25 Mechanism of Action

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

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

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

39 Pharmacokinetics

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

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

52 Metabolism and Elimination

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

60 Elimination is predominately in the feces, mostly as metabolites. Based on the
61 recovery of compound(s) after an oral ¹⁴C-labeled dose of imatinib, approximately 81% of the
62 dose was eliminated within 7 days, in feces (68% of dose) and urine (13% of dose).

63 Unchanged imatinib accounted for 25% of the dose (5% urine, 20% feces), the remainder
64 being metabolites.

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

70 **Special Populations**

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

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

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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

101 ULN=upper limit of normal for the institution

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

107 **Drug-Drug Interactions**

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

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

115 **CYP3A4 Inducers:** Pretreatment of 14 healthy volunteers with multiple doses of rifampin,
 116 600 mg daily for 8 days, followed by a single 400-mg dose of Gleevec, increased Gleevec
 117 oral-dose clearance by 3.8-fold (90% confidence interval = 3.5- to 4.3-fold), which represents
 118 mean decreases in C_{max} , $AUC_{(0-24)}$ and $AUC_{(0-\infty)}$ by 54%, 68% and 74%, of the respective
 119 values without rifampin treatment. (See PRECAUTIONS and DOSAGE AND
 120 ADMINISTRATION.)

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

125 CLINICAL STUDIES

126 Chronic Myeloid Leukemia

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

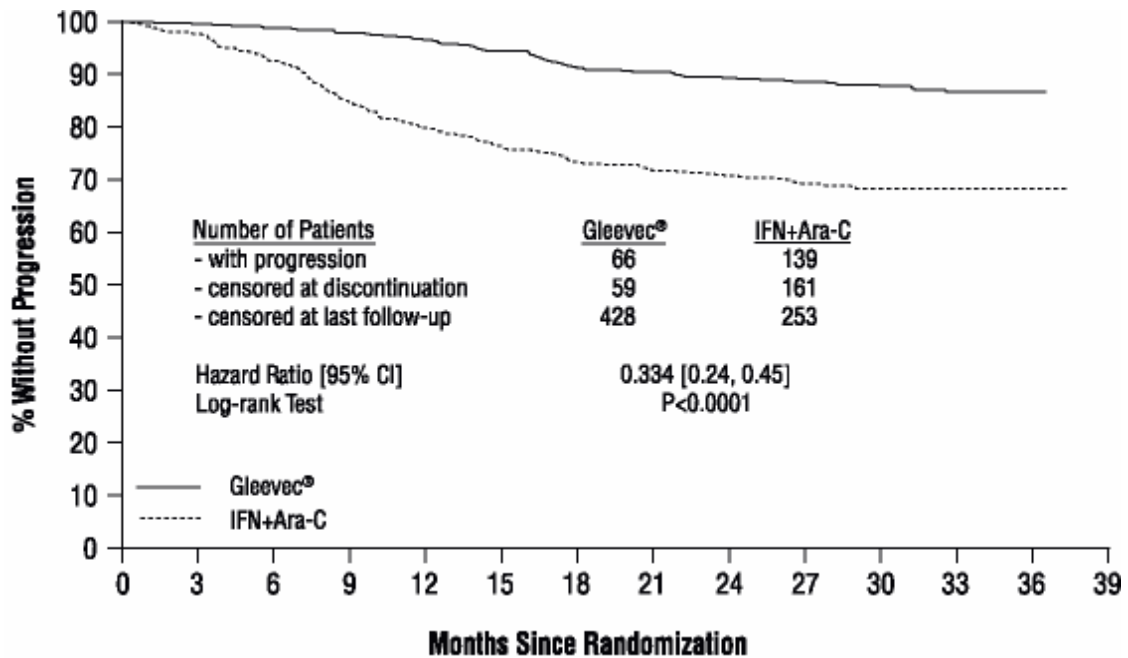
140 A total of 1,106 patients were randomized from 177 centers in 16 countries, 553 to
141 each arm. Baseline characteristics were well balanced between the two arms. Median age was
142 51 years (range 18-70 years), with 21.9% of patients ≥60 years of age. There were 59% males
143 and 41% females; 89.9% Caucasian and 4.7% Black patients. With a median follow-up of 31
144 and 30 months for Gleevec and IFN, respectively, 79% of patients randomized to Gleevec
145 were still receiving first-line treatment. Due to discontinuations and cross-overs, only 7% of
146 patients randomized to IFN were still on first-line treatment. In the IFN arm, withdrawal of
147 consent (13.6%) was the most frequent reason for discontinuation of first-line therapy, and the
148 most frequent reason for cross over to the Gleevec arm was severe intolerance to treatment
149 (25.1%).

150 The primary efficacy endpoint of the study was progression-free survival (PFS).
151 Progression was defined as any of the following events: progression to accelerated phase or
152 blast crisis, death, loss of CHR or MCyR, or in patients not achieving a CHR an increasing
153 WBC despite appropriate therapeutic management. The protocol specified that the
154 progression analysis would compare the intent to treat (ITT) population: patients randomized
155 to receive Gleevec were compared with patients randomized to receive interferon. Patients
156 that crossed over prior to progression were not censored at the time of cross-over, and events
157 that occurred in these patients following cross-over were attributed to the original randomized
158 treatment. The estimated rate of progression-free survival at 30 months in the ITT population
159 was 87.8% in the Gleevec arm and 68.3% in the IFN arm (p<0.001), (Figure 1). The estimated
160 rate of patients free of progression to accelerated phase (AP) or blast crisis (BC) at 30 months
161 was 94.8% in the Gleevec arm compared to the 89.6%, (p=0.0016) in the IFN arm, (Figure 2).
162 There were 33 and 46 deaths reported in the Gleevec and IFN arm, respectively, with an
163 estimated 30-month survival rate of 94.6% and 91.6%, respectively (differences not
164 significant). The probability of remaining progression-free at 30 months was 100% for
165 patients who were in complete cytogenetic response with major molecular response (≥3-log
166 reduction in bcr-abl transcripts as measured by quantitative reverse transcriptase polymerase
167 chain reaction) at 12 months, compared to 93% for patients in complete cytogenetic response

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

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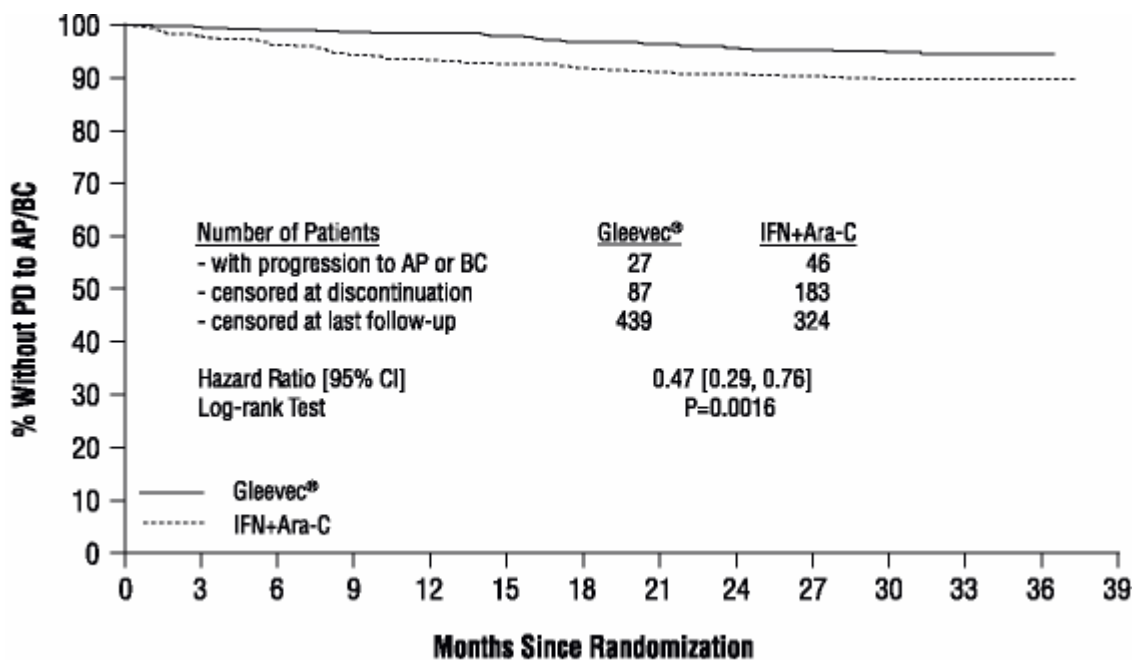
171 **Figure 1 Time to Progression (ITT)**



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



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Major cytogenetic response, hematologic response, evaluation of minimal residual disease (molecular response), time to accelerated phase or blast crisis and survival were main

178 secondary endpoints. Response data are shown in Table 2. Complete hematologic response,
179 major cytogenetic response and complete cytogenetic response were also statistically
180 significantly higher in the Gleevec arm compared to the IFN + Ara-C arm.

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

(Best Response Rate)	Gleevec® n=553	IFN+Ara-C n=553
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

196 * p<0.001, Fischer's exact test

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

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

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

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

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

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

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

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

222 **Chronic Phase, Prior Interferon-Alpha Treatment:** 532 patients were treated at a starting
223 dose of 400 mg; dose escalation to 600 mg was allowed. The patients were distributed in three
224 main categories according to their response to prior interferon: failure to achieve (within 6
225 months), or loss of a complete hematologic response (29%), failure to achieve (within 1 year)
226 or loss of a major cytogenetic response (35%), or intolerance to interferon (36%). Patients had
227 received a median of 14 months of prior IFN therapy at doses $\geq 25 \times 10^6$ IU/week and were all
228 in late chronic phase, with a median time from diagnosis of 32 months. Effectiveness was
229 evaluated on the basis of the rate of hematologic response and by bone marrow exams to
230 assess the rate of major cytogenetic response (up to 35% Ph+ metaphases) or complete
231 cytogenetic response (0% Ph+ metaphases). Median duration of treatment was 29 months
232 with 81% of patients treated for ≥ 24 months (maximum = 31.5 months). Efficacy results are
233 reported in Table 2. Confirmed major cytogenetic response rates were higher in patients with
234 IFN intolerance (66%) and cytogenetic failure (64%), than in patients with hematologic
235 failure (47%). Hematologic response was achieved in 98% of patients with cytogenetic
236 failure, 94% of patients with hematologic failure, and 92% of IFN-intolerant patients.

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

241 Effectiveness was evaluated primarily on the basis of the rate of hematologic response,
242 reported as either complete hematologic response, no evidence of leukemia (i.e., clearance of
243 blasts from the marrow and the blood, but without a full peripheral blood recovery as for
244 complete responses), or return to chronic phase CML. Cytogenetic responses were also
245 evaluated. Median duration of treatment was 18 months with 45% of patients treated for ≥ 24
246 months (maximum=35 months). Efficacy results are reported in Table 3. Response rates in
247 accelerated phase CML were higher for the 600-mg dose group than for the 400-mg group:
248 hematologic response (75% vs. 64%), confirmed and unconfirmed major cytogenetic response
249 (31% vs. 19%).

250 **Myeloid Blast Crisis:** 260 patients with myeloid blast crisis were enrolled. These patients had
251 $\geq 30\%$ blasts in PB or BM and/or extramedullary involvement other than spleen or liver; 95
252 (37%) had received prior chemotherapy for treatment of either accelerated phase or blast
253 crisis ("pretreated patients") whereas 165 (63%) had not ("untreated patients"). The first 37
254 patients were started at 400 mg; the remaining 223 patients were started at 600 mg.

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

265 **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%}]		
271 Hematologic Response¹	95% [92.3-96.3]	71%[64.8-76.8]	31% [25.2-36.8]
272 Complete Hematologic			
273 Response (CHR)	95%	38%	7%
274 No Evidence of Leukemia (NEL)	Not applicable	13%	5%
275 Return to Chronic			
276 Phase (RTC)	Not applicable	20%	18%
277 Major Cytogenetic Response²	60% [55.3-63.8]	21% [16.2-27.1]	7% [4.5-11.2]
278 (Unconfirmed ³)	(65%)	(27%)	(15%)
279 Complete ⁴ (Unconfirmed ³)	39% (47%)	16% (20%)	2% (7%)

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

282 CHR: Chronic phase study [WBC <10 x 10⁹/L, platelet <450 x 10⁹/L, myelocytes + metamyelocytes
283 <5% in blood, no blasts and promyelocytes in blood, basophils <20%, no extramedullary
284 involvement] and in the accelerated and blast crisis studies [ANC ≥1.5 x 10⁹/L, platelets ≥100 x
285 10⁹/L, no blood blasts, BM blasts <5% and no extramedullary disease]

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

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

290 BM=bone marrow, PB=peripheral blood

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

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

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

298 The median time to hematologic response was 1 month. In late chronic phase CML,
299 with a median time from diagnosis of 32 months, an estimated 87.8% of patients who
300 achieved MCyR maintained their response 2 years after achieving their initial response. After
301 2 years of treatment, an estimated 85.4% of patients were free of progression to AP or BC ,
302 and estimated overall survival was 90.8% [88.3, 93.2]. In accelerated phase, median duration
303 of hematologic response was 28.8 months for patients with an initial dose of 600 mg (16.5
304 months for 400 mg, p=0.0035). An estimated 63.8% of patients who achieved MCyR were
305 still in response 2 years after achieving initial response. The median survival was 20.9 [13.1,
306 34.4] months for the 400-mg group and was not yet reached for the 600-mg group (p=0.0097).
307 An estimated 46.2% [34.7, 57.7] vs. 65.8% [58.4, 73.3] of patients were still alive after 2
308 years of treatment in the 400-mg vs. 600-mg dose groups, respectively (p=0.0088). In blast
309 crisis, the estimated median duration of hematologic response is 10 months. An estimated
310 27.2% [16.8, 37.7] of hematologic responders maintained their response 2 years after

311 achieving their initial response. Median survival was 6.9 [5.8, 8.6] months, and an estimated
312 18.3% [13.4, 23.3] of all patients with blast crisis were alive 2 years after start of study.

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

316 **Pediatric CML:** One open-label, single-arm study enrolled 14 pediatric patients with Ph+
317 chronic phase CML recurrent after stem cell transplant or resistant to interferon-alpha therapy.
318 Patients ranged in age from 3-20 years old; 3 were 3-11 years old, 9 were 12-18 years old, and
319 2 were >18 years old. Patients were treated at doses of 260 mg/m²/day (n=3), 340 mg/m²/day
320 (n=4), 440 mg/m²/day (n=5) and 570 mg/m²/day (n=2). In the 13 patients for whom
321 cytogenetic data are available, 4 achieved a major cytogenetic response, 7 achieved a
322 complete cytogenetic response, and 2 had a minimal cytogenetic response. At the
323 recommended dose of 260 mg/m²/day, 2 of 3 patients achieved a complete cytogenetic
324 response. Cytogenetic response rate was similar at all dose levels.

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

327 **Gastrointestinal Stromal Tumors**

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

337 The primary outcome of the study was objective response rate. Tumors were required
338 to be measurable at entry in at least one site of disease, and response characterization was
339 based on Southwestern Oncology Group (SWOG) criteria. . Results are shown in Table 4.

340 **Table 4 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)

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

345 **INDICATIONS AND USAGE**

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

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

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

362 **CONTRAINDICATIONS**

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

365 **WARNINGS**

366 **Pregnancy**

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

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

377 Male and female rats were exposed *in utero* to a maternal imatinib mesylate dose of
378 45 mg/kg (approximately one-half the maximum human dose of 800 mg) from Day 6 of
379 gestation and through milk during the lactation period. These animals then received no
380 imatinib exposure for nearly 2 months. Body weights were reduced from birth until terminal
381 sacrifice in these rats. Although fertility was not affected, fetal loss was seen when these male
382 and female animals were then mated.

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

386 PRECAUTIONS

387 General

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

396 ***Fluid Retention and Edema:*** Gleevec is often associated with edema and occasionally
397 serious fluid retention (see ADVERSE REACTIONS). Patients should be weighed and
398 monitored regularly for signs and symptoms of fluid retention. An unexpected rapid weight
399 gain should be carefully investigated and appropriate treatment provided. The probability of
400 edema was increased with higher Gleevec dose and age >65 years in the CML studies. Severe
401 superficial edema was reported in 1.1% of newly diagnosed CML patients taking Gleevec,
402 and in 2%-6% of other adult CML patients taking Gleevec. In addition, other severe fluid
403 retention (e.g., pleural effusion, pericardial effusion, pulmonary edema, and ascites) events
404 were reported in 0.7% of newly diagnosed CML patients taking Gleevec, and in 2%-6% of
405 other adult CML patients taking Gleevec. Severe superficial edema and severe fluid retention
406 (pleural effusion, pulmonary edema and ascites) were reported in 1%-6% of patients taking
407 Gleevec for GIST.

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

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

413 ***Hemorrhage:*** In the newly diagnosed CML trial, 1.1% of patients had Grade 3/4
414 hemorrhage. In the GIST clinical trial, seven patients (5%), four in the 600-mg dose group
415 and three in the 400-mg dose group, had a total of eight events of CTC Grade 3/4 -

416 gastrointestinal (GI) bleeds (3 patients), intra-tumoral bleeds (3 patients) or both (1 patient).
417 Gastrointestinal tumor sites may have been the source of GI bleeds.

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

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

429 **Hepatic impairment:** Comparable exposure was noted between each of the mildly and
430 moderately hepatically impaired patients and patients with normal hepatic function. However,
431 patients with severe hepatic impairment tended to have higher exposure to both imatinib and
432 its metabolite than patients with normal hepatic function (See CLINICAL
433 PHARMACOLOGY and DOSING AND ADMINISTRATION). Patients with severe hepatic
434 impairment should be closely monitored.

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

445 **Drug Interactions**

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

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

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

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

454 Substances that are inducers of CYP3A4 activity may increase metabolism and decrease
455 imatinib plasma concentrations. Co-medications that induce CYP3A4 (e.g., dexamethasone,

456 phenytoin, carbamazepine, rifampin, phenobarbital or St. John's Wort) may significantly
457 reduce exposure to Gleevec. Pretreatment of healthy volunteers with multiple doses of
458 rifampin followed by a single dose of Gleevec, increased Gleevec oral-dose clearance by
459 3.8-fold, which significantly ($p < 0.05$) decreased mean C_{max} and $AUC_{(0-\infty)}$. In patients where
460 rifampin or other CYP3A4 inducers are indicated, alternative therapeutic agents with less
461 enzyme induction potential should be considered. (See CLINICAL PHARMACOLOGY and
462 DOSAGE AND ADMINISTRATION.)

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

464 Gleevec increases the mean C_{max} and AUC of simvastatin (CYP3A4 substrate) 2- and
465 3.5-fold, respectively, suggesting an inhibition of the CYP3A4 by Gleevec. Particular caution
466 is recommended when administering Gleevec with CYP3A4 substrates that have a narrow
467 therapeutic window (e.g., cyclosporine or pimozide). Gleevec will increase plasma
468 concentration of other CYP3A4 metabolized drugs (e.g., triazolo-benzodiazepines,
469 dihydropyridine calcium channel blockers, certain HMG-CoA reductase inhibitors, etc.).

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

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

476 *In vitro*, Gleevec inhibits acetaminophen O-glucuronidation (K_i value of 58.5 μM) at
477 therapeutic levels. Systemic exposure to acetaminophen is expected to be increased when
478 coadministered with Gleevec. No specific studies in humans have been performed and caution
479 is recommended.

480 **Carcinogenesis, Mutagenesis, Impairment of Fertility**

481 The urogenital tract from a 2-year carcinogenicity study in rats receiving doses of 15, 30 and
482 60 mg/kg/day of imatinib mesylate showed renal adenomas/carcinomas, urinary bladder
483 papillomas and papillomas/carcinomas of the preputial and clitoral gland. Evaluation of other
484 organs in the rats is ongoing.

485 The papilloma/carcinoma of the preputial/clitoral gland were noted at 30 and
486 60 mg/kg/day (approximately 0.5 to 4 times the human daily exposure at 400 mg/day). The
487 kidney adenoma/carcinoma and the urinary bladder papilloma were noted at 60 mg/kg/day.
488 No tumors in the urogenital tract were observed at 15 mg/kg/day.

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

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

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

505 **Pregnancy**

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

507 **Nursing Mothers**

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

517 **Pediatric Use**

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

521 **Geriatric Use**

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

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

532 **ADVERSE REACTIONS**533 **Chronic Myeloid Leukemia**

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

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

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

552 Adverse events, regardless of relationship to study drug, that were reported in at least
 553 10% of the patients treated in the Gleevec studies are shown in Tables 5 and 6.

554 **Table 5 Adverse Experiences Reported in Newly Diagnosed CML Clinical Trial (≥10% of**
 555 **all patients)⁽¹⁾**

556 Preferred Term	557 All Grades		558 CTC Grades 3/4	
	559 Gleevec [®] N=551 (%)	560 IFN+Ara-C N=533 (%)	561 Gleevec [®] N=551 (%)	562 IFN+Ara-C N=533 (%)
563 Fluid Retention	59.2	10.7	1.8	0.9
564 - Superficial Edema	57.5	9.2	1.1	0.4
565 - Other Fluid Retention Events	6.9	1.9	0.7	0.6
566 Nausea	47.0	61.5	0.9	5.1
567 Muscle Cramps	43.2	11.4	1.6	0.2
568 Musculoskeletal Pain	39.2	44.1	3.4	8.1
569 Diarrhea	38.5	42.0	2.0	3.2
570 Rash and Related Terms	37.2	25.7	2.4	2.4
571 Fatigue	37.0	66.8	1.6	25.0
572 Headache	33.6	43.3	0.5	3.6
573 Joint Pain	30.3	39.4	2.5	7.3
574 Abdominal Pain	29.9	25.0	2.5	3.9
575 Nasopharyngitis	26.9	8.4	0	0.2
576 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

577	Vomiting	20.5	27.4	1.5	3.4
578	Dyspepsia	17.8	9.2	0	0.8
579	Cough	17.4	23.1	0.2	0.6
580	Pharyngolaryngeal Pain	16.9	11.3	0.25	0
581	Upper Respiratory Tract Infection	16.5	8.4	0.2	0.4
582	Dizziness	15.8	24.2	0.9	3.6
583	Pyrexia	15.4	42.4	0.9	3.0
584	Weight Increased	15.2	2.1	1.6	0.4
585	Insomnia	13.2	18.8	0	2.3
586	Depression	12.7	35.8	0.5	13.1
587	Influenza	11.1	6.0	0.2	0.2

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

590 **Table 6 Adverse Experiences Reported in Other CML Clinical Trials ($\geq 10\%$ of all patients in any**
 591 **trial)⁽¹⁾**

596 597 598 599 600 601 602 603 604 605 606 607 608 609 610 611 612 613 614 615 616 617 618 619 620 621 622 623 624 625 626 627 628 629 630 631 632 633 634 635 636 637	Myeloid Blast		Accelerated		Chronic Phase,	
	Crisis		Phase		IFN Failure	
	(n= 260)		(n=235)		(n=532)	
	%		%		%	
	All	Grade	All	Grade	All	Grade
Preferred Term	Grades	3/4	Grades	3/4	Grades	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

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

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

Hematologic Toxicity

642
643 Cytopenias, and particularly neutropenia and thrombocytopenia, were a consistent finding in
644 all studies, with a higher frequency at doses ≥ 750 mg (Phase 1 study). However, the
645 occurrence of cytopenias in CML patients was also dependent on the stage of the disease.

646 In patients with newly diagnosed CML, cytopenias were less frequent than in the other
647 CML patients (see Tables 7 and 8). The frequency of grade 3 or 4 neutropenia and
648 thrombocytopenia was between 2- and 3-fold higher in blast crisis and accelerated phase
649 compared to chronic phase (see Tables 7 and 8). The median duration of the neutropenic and
650 thrombocytopenic episodes varied from 2 to 3 weeks, and from 2 to 4 weeks, respectively.

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

Hepatotoxicity

654 Severe elevation of transaminases or bilirubin occurred in 3%-6% (see Table 7) and were
655 usually managed with dose reduction or interruption (the median duration of these episodes
656 was approximately 1 week). Treatment was discontinued permanently because of liver
657 laboratory abnormalities in less than 0.5% of CML patients. However, one patient, who was
658 taking acetaminophen regularly for fever, died of acute liver failure. In the GIST trial, grade
659 3 or 4 SGPT (ALT) elevations were observed in 6.8% of patients and grade 3 or 4 SGOT
660 (AST) elevations were observed in 4.8% of patients. Bilirubin elevation was observed in
661 2.7% of patients.
662
663

Adverse Reactions in Pediatric Population

664 The overall safety profile of pediatric patients treated with Gleevec in 39 children studied was
665 similar to that found in studies with adult patients, except that musculoskeletal pain was less
666 frequent (20.5%) and peripheral edema was not reported.
667

Adverse Effects in Other Subpopulations

668 In older patients (≥ 65 years old), with the exception of edema, where it was more frequent,
669 there was no evidence of an increase in the incidence or severity of adverse events. In women
670 there was an increase in the frequency of neutropenia, as well as Grade 1/2 superficial edema,
671 headache, nausea, rigors, vomiting, rash, and fatigue. No differences were seen related to race
672 but the subsets were too small for proper evaluation.
673

674 **Table 7 Lab Abnormalities in Newly Diagnosed CML Trial**

	Gleevec® N=551 %		IFN+Ara-C N=533 %	
CTC Grades	Grade 3	Grade 4	Grade 3	Grade 4
Hematology Parameters				
- Neutropenia*	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

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

691 **Table 8 Lab Abnormalities in Other CML Clinical Trials**

	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 %	
CTC Grades	Grade 3	Grade 4	Grade 3	Grade 4	Grade 3	Grade 4
Hematology Parameters						
- Neutropenia	16	48	23	36	27	9
- Thrombocytopenia	30	33	31	13	21	<1
- Anemia	42	11	34	7	6	1
Biochemistry Parameters						
- Elevated Creatinine	1.5	0	1.3	0	0.2	0
- Elevated Bilirubin	3.8	0	2.1	0	0.6	0
- Elevated Alkaline Phosphatase	4.6	0	5.5	0.4	0.2	0
- Elevated SGOT (AST)	1.9	0	3.0	0	2.3	0
- Elevated SGPT (ALT)	2.3	0.4	4.3	0	2.1	0

711 CTC Grades: neutropenia (Grade 3 $\geq 0.5-1.0 \times 10^9/L$, Grade 4 $< 0.5 \times 10^9/L$), thrombocytopenia (Grade
 712 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
 713 creatinine (Grade 3 $> 3-6$ x upper limit normal range [ULN], Grade 4 > 6 x ULN), elevated bilirubin
 714 (Grade 3 $> 3-10$ x ULN, Grade 4 > 10 x ULN), elevated alkaline phosphatase (Grade 3 $> 5-20$ x ULN,
 715 Grade 4 > 20 x ULN), elevated SGOT or SGPT (Grade 3 $> 5-20$ x ULN, Grade 4 > 20 x ULN)

716 **Gastrointestinal Stromal Tumors**

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

719 cramps, fatigue, and rash. Most events were of mild-to-moderate severity. Drug was
 720 discontinued for adverse events in 7 patients (5%) in both dose levels studied. Superficial
 721 edema, most frequently periorbital or lower extremity edema, was managed with diuretics,
 722 other supportive measures, or by reducing the dose of Gleevec® (imatinib mesylate).
 723 (See DOSAGE AND ADMINISTRATION.) Severe (CTC Grade 3/4) superficial edema was
 724 observed in 3 patients (2%), including face edema in one patient. Grade 3/4 pleural effusion
 725 or ascites was observed in 3 patients (2%).

726 Adverse events, regardless of relationship to study drug, that were reported in at least
 727 10% of the patients treated with Gleevec are shown in Table 9. No major differences were
 728 seen in the severity of adverse events between the 400-mg or 600-mg treatment groups,
 729 although overall incidence of diarrhea, muscle cramps, headache, dermatitis, and edema was
 730 somewhat higher in the 600-mg treatment group.

731 **Table 9 Adverse Experiences Reported in GIST Trial (≥10% of all patients at either dose)⁽¹⁾**
 732

Preferred Term	All CTC Grades		CTC Grade 3/4	
	Initial dose (mg/day)		Initial dose (mg/day)	
	400 mg (n=73)	600 mg (n=74)	400 mg (n=73)	600 mg (n=74)
	%	%	%	%
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
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⁽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.

733 Clinically relevant or severe abnormalities of routine hematologic or biochemistry
734 laboratory values are presented in Table 10.

735 **Table 10 Laboratory Abnormalities in GIST Trial**

736	737	400 mg		600 mg	
		(n=73)		(n=74)	
738	739	%		%	
740	CTC Grades	Grade 3	Grade 4	Grade 3	Grade 4
740	Hematology Parameters				
741	- Anemia	3	0	8	1
742	- Thrombocytopenia	0	0	1	0
743	- Neutropenia	7	3	8	3
744	Biochemistry Parameters				
745	- Elevated Creatinine	0	0	3	0
746	- Reduced Albumin	3	0	4	0
747	- Elevated Bilirubin	1	0	1	3
748	- Elevated Alkaline Phosphatase	0	0	3	0
749	- Elevated SGOT (AST)	4	0	3	3
750	- Elevated SGPT (ALT)	6	0	7	1

751 CTC Grades: neutropenia (Grade 3 $\geq 0.5-1.0 \times 10^9/L$, Grade 4 $< 0.5 \times 10^9/L$), thrombocytopenia (Grade
752 3 $\geq 10 - 50 \times 10^9/L$, Grade 4 $< 10 \times 10^9/L$), anemia (Grade 3 $\geq 65-80$ g/L, grade 4 < 65 g/L), elevated
753 creatinine (Grade 3 $> 3-6$ x upper limit normal range [ULN], Grade 4 > 6 x ULN), elevated bilirubin
754 (Grade 3 $> 3-10$ x ULN, Grade 4 > 10 x ULN), elevated alkaline phosphatase, SGOT or SGPT (Grade 3
755 $> 5-20$ x ULN, Grade 4 > 20 x ULN), albumin (Grade 3 < 20 g/L)

756 Additional Data From Multiple Clinical Trials

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

760 **Cardiovascular:** *Infrequent:* cardiac failure, tachycardia, hypertension, hypotension, flushing,
761 peripheral coldness

762 *Rare:* pericarditis

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

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

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

767 *Rare:* vesicular rash, Stevens-Johnson syndrome, acute generalized exanthematous pustulosis

768 **Digestive:** *Less common:* abdominal distention, gastroesophageal reflux, mouth ulceration

769 *Infrequent:* gastric ulcer, gastroenteritis, gastritis

770 *Rare:* colitis, ileus/intestinal obstruction, pancreatitis

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

772 **Hematologic:** *Infrequent:* pancytopenia

773 *Rare:* aplastic anemia

774 **Hypersensitivity:** *Rare:* angioedema

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

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

793 OVERDOSAGE

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

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

807 DOSAGE AND ADMINISTRATION

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

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

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

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

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

825 For patients unable to swallow the film-coated tablets, the tablets may be dispersed in
826 a glass of water or apple juice. The required number of tablets should be placed in the
827 appropriate volume of beverage (approximately 50 mL for a 100-mg tablet, and 200 mL for a
828 400-mg tablet) and stirred with a spoon. The suspension should be administered immediately
829 after complete disintegration of the tablet(s).

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

832 In CML, a dose increase from 400 mg to 600 mg in adult patients with chronic phase
833 disease, or from 600 mg to 800 mg (given as 400 mg twice daily) in adult patients in
834 accelerated phase or blast crisis may be considered in the absence of severe adverse drug
835 reaction and severe non-leukemia related neutropenia or thrombocytopenia in the following
836 circumstances: disease progression (at any time), failure to achieve a satisfactory hematologic
837 response after at least 3 months of treatment, failure to achieve a cytogenetic response after
838 6-12 months of treatment, or loss of a previously achieved hematologic or cytogenetic
839 response. In children with chronic phase CML, daily doses can be increased under
840 circumstances similar to those leading to an increase in adult chronic phase disease, from
841 $260 \text{ mg/m}^2/\text{day}$ to $340 \text{ mg/m}^2/\text{day}$, as clinically indicated.

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

845 For daily dosing of 800 mg and above, dosing should be accomplished using the
846 400-mg tablet to reduce exposure to iron.

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

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

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

856 400 mg). In children, daily doses can be reduced under the same circumstances from
857 260 mg/m²/day to 200 mg/m²/day or from 340 mg/m²/day to 260 mg/m²/day, respectively.

858 Dose Adjustment for Hematologic Adverse Reactions

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

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

862 Chronic Phase CML 863 (starting dose 400mg ¹) 864 865 or GIST 866 (starting dose either 867 400 mg or 600 mg) 868 869 870 871 872 873 874 875	ANC <1.0 x 10 ⁹ /L and/or Platelets <50 x 10 ⁹ /L	1. Stop Gleevec until ANC ≥1.5 x 10 ⁹ /L and platelets ≥75 x 10 ⁹ /L 2. Resume treatment with Gleevec at the original starting dose of 400 mg ¹ or 600 mg 3. If recurrence of ANC <1.0 x 10 ⁹ /L and/or platelets <50 x 10 ⁹ /L, repeat step 1 and resume Gleevec at a reduced dose (300 mg ² if starting dose was 400 mg ¹ , 400 mg if starting dose was 600 mg)
876 Accelerated Phase 877 CML and Blast Crisis 878 (starting dose 600 mg) 879 880 881 882 883 884 885 886 887 888 889	³ ANC <0.5 x 10 ⁹ /L and/or Platelets <10 x 10 ⁹ /L	1. Check if cytopenia is related to leukemia (marrow aspirate or biopsy) 2. If cytopenia is unrelated to leukemia, reduce dose of Gleevec to 400 mg 3. If cytopenia persists 2 weeks, reduce further to 300 mg 4. If cytopenia persists 4 weeks and is still unrelated to leukemia, stop Gleevec until ANC ≥1 x 10 ⁹ /L and platelets ≥20 x 10 ⁹ /L and then resume treatment at 300 mg

890 ¹ or 260 mg/m² in children

891 ² or 200 mg/m² in children

892 ³occurring after at least 1 month of treatment

893

894

895 HOW SUPPLIED

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

897 100-mg Tablets

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

900 Bottles of 100 tabletsNDC 0078-0401-05

901 **400-mg Tablets**

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

905 Bottles of 30 tabletsNDC 0078-0438-15

906 **Storage**

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

909 Dispense in a tight container, USP.

910 T2005-18
911 REV: MARCH 2005 Printed in U.S.A. 5000305

912

913  **NOVARTIS**

914

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916 Novartis Pharma Stein AG
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