

## HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use Gleevec safely and effectively. See full prescribing information for Gleevec.

**GLEEVEC (imatinib mesylate) tablets for oral use**  
**Initial U.S. Approval: 2001**

### RECENT MAJOR CHANGES

Indications and Usage Newly Diagnosed Ph+ CML (1.1)	XX/2009
Indications and Usage: GIST (1.9)	09/2008
Indications and Usage Adjuvant treatment of GIST (1.10)	12/2008
Dosage and Administration: GIST (2.8)	09/2008
Dosage and Administration Adjuvant treatment of GIST (2.8)	12/2008
Dose Modification Guidelines: Renal Impairment (2.9)	09/2008
Warnings and Precautions: Hepatotoxicity (5.4), Hemorrhage (5.5), Hypothyroidism (5.9)	09/2008

### INDICATIONS AND USAGE

Gleevec is a kinase inhibitor indicated for the treatment of:

- Newly diagnosed adult patients with Philadelphia chromosome positive chronic myeloid leukemia (Ph+ CML) in chronic phase.
- Patients with Philadelphia chromosome positive chronic myeloid leukemia (Ph+ CML) in blast crisis (BC), accelerated phase (AP), or in chronic phase (CP) after failure of interferon-alpha therapy (1.2)
- Pediatric patients with Ph+ CML in chronic phase who are newly diagnosed or whose disease has recurred after stem cell transplant or who are resistant to interferon-alpha therapy. There are no controlled trials in pediatric patients demonstrating a clinical benefit, such as improvement in disease-related symptoms or increased survival (1.3)
- Adult patients with relapsed or refractory Philadelphia chromosome positive acute lymphoblastic leukemia (Ph+ ALL) (1.4)
- Adult patients with myelodysplastic/myeloproliferative diseases (MDS/MPD) associated with PDGFR (platelet-derived growth factor receptor) gene re-arrangements (1.5)
- Adult patients with aggressive systemic mastocytosis (ASM) without the D816V c-Kit mutation or with c-Kit mutational status unknown (1.6)
- Adult patients with hypereosinophilic syndrome (HES) and/or chronic eosinophilic leukemia (CEL) who have the FIP1L1-PDGFR $\alpha$  fusion kinase (mutational analysis or FISH demonstration of CHIC2 allele deletion) and for patients with HES and/or CEL who are FIP1L1-PDGFR $\alpha$  fusion kinase negative or unknown (1.7)
- Adult patients with unresectable, recurrent and/or metastatic dermatofibrosarcoma protuberans (DFSP) (1.8)
- Patients with Kit (CD117) positive unresectable and/or metastatic malignant gastrointestinal stromal tumors (GIST). (1.9)
- Adjuvant treatment of adult patients following resection of Kit (CD117) positive GIST (1.10)

### DOSAGE AND ADMINISTRATION

• Adults with Ph+ CML CP (2.1):	400 mg/day
• Adults with Ph+ CML AP or BC (2.1):	600 mg/day
• Pediatrics with Ph+ CML (2.2):	340 mg/m <sup>2</sup> /day or 260 mg/m <sup>2</sup> /day
• Adults with Ph+ ALL (2.3):	600 mg/day
• Adults with MDS/MPD (2.4):	400 mg/day
• Adults with ASM (2.5):	100 mg/day or 400 mg/day
• Adults with HES/CEL (2.6):	100 mg/day or 400 mg/day
• Adults with DFSP (2.7):	800 mg/day
• Adults with metastatic and/or unresectable GIST (2.8):	400 mg/day
• Adjuvant treatment of adults with GIST (2.8):	400 mg/day
• Patients with mild to moderate hepatic impairment (2.9):	400 mg/day
• Patients with severe hepatic impairment (2.9):	300 mg/day

All doses of Gleevec should be taken with a meal and a large glass of water. Doses of 400 mg or 600 mg should be administered once daily, whereas a dose of 800 mg should be administered as 400 mg twice a day. Gleevec can be dissolved in water or apple juice for patients having difficulty swallowing. Daily dosing of 800 mg and above should be accomplished using the 400 mg tablet to reduce exposure to iron.

### DOSAGE FORMS AND STRENGTHS

Tablets (scored): 100 mg and 400 mg (3)

### CONTRAINDICATIONS

None (4)

### WARNINGS AND PRECAUTIONS

- Edema and severe fluid retention have occurred. Weigh patients regularly and manage unexpected rapid weight gain by drug interruption and diuretics (5.1, 6.1, 6.11)
- Cytopenias, particularly anemia, neutropenia, and thrombocytopenia, have occurred. Manage with dose reduction or dose interruption and in rare cases discontinuation of treatment. Perform complete blood counts weekly for the first month, biweekly for the second month, and periodically thereafter (5.2)
- Severe congestive heart failure and left ventricular dysfunction have been reported, particularly in patients with comorbidities and risk factors. Patients with cardiac disease or risk factors for cardiac failure should be monitored and treated (5.3)
- Severe hepatotoxicity may occur. Assess liver function before initiation of treatment and monthly thereafter or as clinically indicated. Monitor liver function when combined with chemotherapy known to be associated with liver dysfunction (5.4)
- Grade 3/4 hemorrhage has been reported in clinical studies in patients with newly diagnosed CML and with GIST. GI tumor sites may be the source of GI bleeds in GIST (5.5)
- Gastrointestinal perforations, some fatal, have been reported (5.6)
- Cardiogenic shock/left ventricular dysfunction has been associated with the initiation of Gleevec in patients with conditions associated with high eosinophil levels (e.g., HES, MDS/MPD and ASM) (5.7)
- Bullous dermatologic reactions (e.g., erythema multiforme and Stevens-Johnson syndrome) have been reported with the use of Gleevec (5.8)
- Hypothyroidism has been reported in thyroidectomy patients undergoing levothyroxine replacement. Closely monitor TSH levels in such patients (5.9).
- Consider potential toxicities, specifically, liver, kidney, and cardiac toxicity, and immunosuppression from long-term use (5.10)
- Fetal harm can occur when administered to a pregnant woman. Women should be apprised of the potential harm to the fetus (5.11, 8.1)

### ADVERSE REACTIONS

The most frequently reported adverse reactions ( $\geq 30\%$ ) were edema, nausea, vomiting, muscle cramps, musculoskeletal pain, diarrhea, rash, fatigue and abdominal pain (6.1, 6.11)

**To report SUSPECTED ADVERSE REACTIONS, contact Novartis Pharmaceuticals Corporation at 1-888-669-6682 or FDA at 1-800-FDA-1088 or [www.fda.gov/medwatch](http://www.fda.gov/medwatch)**

### DRUG INTERACTIONS

- CYP3A4 inducers may decrease Gleevec C<sub>max</sub> and AUC (2.9, 7.1)
- CYP3A4 inhibitors may increase Gleevec C<sub>max</sub> and AUC (7.2)
- Gleevec is an inhibitor of CYP3A4 and may increase the C<sub>max</sub> and AUC of other drugs (7.3)
- Patients who require anticoagulation should receive low-molecular weight or standard heparin and not warfarin (7.3)
- Systemic exposure to acetaminophen is expected to increase when co-administered with Gleevec (7.5)

### USE IN SPECIFIC POPULATIONS

- There is no experience in children less than 2 years of age (8.4)

See 17 for PATIENT COUNSELING INFORMATION

Revised: 05/2009

## FULL PRESCRIBING INFORMATION: CONTENTS\*

### 1 INDICATIONS AND USAGE

- 1.1 Newly Diagnosed Philadelphia Positive Chronic Myeloid Leukemia (Ph+ CML)
- 1.2 Ph+ CML in Blast Crisis (BC), Accelerated Phase (AP) or Chronic Phase (CP) After Interferon-alpha (IFN) Therapy
- 1.3 Pediatric Patients with Ph+ CML in Chronic Phase
- 1.4 Ph+ Acute Lymphoblastic Leukemia (ALL)
- 1.5 Myelodysplastic/Myeloproliferative Diseases (MDS/MPD)
- 1.6 Aggressive Systemic Mastocytosis (ASM)
- 1.7 Hypereosinophilic Syndrome (HES) and/or Chronic Eosinophilic Leukemia (CEL)
- 1.8 Dermatofibrosarcoma Protuberans (DFSP)
- 1.9 Kit+ Gastrointestinal Stromal Tumors (GIST)
- 1.10 Adjuvant Treatment of GIST

### 2 DOSAGE AND ADMINISTRATION

- 2.1 Adult Patients with Ph+ CML CP, AP and BC
- 2.2 Pediatric Patients with Ph+ CML
- 2.3 Ph+ ALL
- 2.4 MDS/MPD
- 2.5 ASM
- 2.6 HES/CEL
- 2.7 DFSP
- 2.8 GIST
- 2.9 Dose Modification Guidelines
- 2.10 Dose Adjustment for Hepatotoxicity and Non-Hematologic Adverse Reactions
- 2.11 Dose Adjustment for Hematologic Adverse Reactions

### 3 DOSAGE FORMS AND STRENGTHS

### 4 CONTRAINDICATIONS

### 5 WARNINGS AND PRECAUTIONS

- 5.1 Fluid Retention and Edema
- 5.2 Hematologic Toxicity
- 5.3 Severe Congestive Heart Failure and Left Ventricular Dysfunction
- 5.4 Hepatotoxicity
- 5.5 Hemorrhage
- 5.6 Gastrointestinal Disorders
- 5.7 Hypereosinophilic Cardiac Toxicity
- 5.8 Dermatologic Toxicities
- 5.9 Hypothyroidism
- 5.10 Toxicities from Long-Term Use
- 5.11 Use in Pregnancy

### 6 ADVERSE REACTIONS

- 6.1 Chronic Myeloid Leukemia
- 6.2 Hematologic Toxicity
- 6.3 Hepatotoxicity
- 6.4 Adverse Reactions in Pediatric Population
- 6.5 Adverse Reactions in Other Subpopulations

- 6.6 Acute Lymphoblastic Leukemia
- 6.7 Myelodysplastic/Myeloproliferative Diseases
- 6.8 Aggressive Systemic Mastocytosis
- 6.9 Hypereosinophilic Syndrome and Chronic Eosinophilic Leukemia
- 6.10 Dermatofibrosarcoma Protuberans
- 6.11 Gastrointestinal Stromal Tumors
- 6.12 Additional Data from Multiple Clinical Trials
- 6.13 Postmarketing Experience

### 7 DRUG INTERACTIONS

- 7.1 Agents Inducing CYP3A Metabolism
- 7.2 Agents Inhibiting CYP3A Metabolism
- 7.3 Interactions with Drugs Metabolized by CYP3A4
- 7.4 Interactions with Drugs Metabolized by CYP2D6
- 7.5 Interaction with Acetaminophen

### 8 USE IN SPECIFIC POPULATIONS

- 8.1 Pregnancy
- 8.3 Nursing Mothers
- 8.4 Pediatric Use
- 8.5 Geriatric Use
- 8.6 Hepatic Impairment
- 8.7 Renal Impairment

### 10 OVERDOSAGE

### 11 DESCRIPTION

### 12 CLINICAL PHARMACOLOGY

- 12.1 Mechanism of Action
- 12.3 Pharmacokinetics

### 13 NONCLINICAL TOXICOLOGY

- 13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

### 14 CLINICAL STUDIES

- 14.1 Chronic Myeloid Leukemia
- 14.2 Pediatric CML
- 14.3 Acute Lymphoblastic Leukemia
- 14.4 Myelodysplastic/Myeloproliferative Diseases
- 14.5 Aggressive Systemic Mastocytosis
- 14.6 Hypereosinophilic Syndrome/Chronic Eosinophilic Leukemia
- 14.7 Dermatofibrosarcoma Protuberans
- 14.8 Gastrointestinal Stromal Tumors

### 15 REFERENCES

### 16 HOW SUPPLIED/STORAGE AND HANDLING

### 17 PATIENT COUNSELING INFORMATION

- 17.1 Dosing and Administration
- 17.2 Pregnancy and Breast-Feeding
- 17.3 Adverse Reactions
- 17.4 Drug Interactions

\* Sections or subsections omitted from the full prescribing information are not listed

## **FULL PRESCRIBING INFORMATION**

### **1 INDICATIONS AND USAGE**

#### **1.1 Newly Diagnosed Philadelphia Positive Chronic Myeloid Leukemia (Ph+ CML)**

Newly diagnosed adult patients with Philadelphia chromosome positive chronic myeloid leukemia in chronic phase.

#### **1.2 Ph+ CML in Blast Crisis (BC), Accelerated Phase (AP) or Chronic Phase (CP) After Interferon-alpha (IFN) Therapy**

Patients with Philadelphia chromosome positive chronic myeloid leukemia in blast crisis, accelerated phase, or in chronic phase after failure of interferon-alpha therapy.

#### **1.3 Pediatric Patients with Ph+ CML in Chronic Phase**

Pediatric patients with Ph+ CML in chronic phase who are newly diagnosed or whose disease has recurred after stem cell transplant or who are resistant to interferon-alpha therapy. There are no controlled trials in pediatric patients demonstrating a clinical benefit, such as improvement in disease-related symptoms or increased survival.

#### **1.4 Ph+ Acute Lymphoblastic Leukemia (ALL)**

Adult patients with relapsed or refractory Philadelphia chromosome positive acute lymphoblastic leukemia.

#### **1.5 Myelodysplastic/Myeloproliferative Diseases (MDS/MPD)**

Adult patients with myelodysplastic/ myeloproliferative diseases associated with PDGFR (platelet-derived growth factor receptor) gene re-arrangements.

#### **1.6 Aggressive Systemic Mastocytosis (ASM)**

Adult patients with aggressive systemic mastocytosis without the D816V c-Kit mutation or with c-Kit mutational status unknown.

#### **1.7 Hypereosinophilic Syndrome (HES) and/or Chronic Eosinophilic Leukemia (CEL)**

Adult patients with hypereosinophilic syndrome and/or chronic eosinophilic leukemia who have the FIP1L1-PDGFR $\alpha$  fusion kinase (mutational analysis or FISH demonstration of CHIC2 allele deletion) and for patients with HES and/or CEL who are FIP1L1-PDGFR $\alpha$  fusion kinase negative or unknown.

#### **1.8 Dermatofibrosarcoma Protuberans (DFSP)**

Adult patients with unresectable, recurrent and/or metastatic dermatofibrosarcoma protuberans.

#### **1.9 Kit+ Gastrointestinal Stromal Tumors (GIST)**

Patients with Kit (CD117) positive unresectable and/or metastatic malignant gastrointestinal stromal tumors.

#### **1.10 Adjuvant Treatment of GIST**

Adjuvant treatment of adult patients following complete gross resection of Kit (CD117) positive GIST.

### **2 DOSAGE AND ADMINISTRATION**

Therapy should be initiated by a physician experienced in the treatment of patients with hematological malignancies or malignant sarcomas, as appropriate. The prescribed dose should be administered orally, with a meal and a large glass of water. Doses of 400 mg or 600 mg should be administered once daily, whereas a dose of 800 mg should be administered as 400 mg twice a day.

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

For patients unable to swallow the film-coated tablets, the tablets may be dispersed in a glass of water or apple

mL for a 100 mg tablet, and 200 mL for a 400 mg tablet) and stirred with a spoon. The suspension should be administered immediately after complete disintegration of the tablet(s).

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

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

### **2.1 Adult Patients with Ph+ CML CP, AP and BC**

The recommended dose of Gleevec is 400 mg/day for adult patients in chronic phase CML and 600 mg/day for adult patients in accelerated phase or blast crisis.

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

### **2.2 Pediatric Patients with Ph+ CML**

The recommended dose of Gleevec for children with newly diagnosed Ph+ CML is 340 mg/m<sup>2</sup>/day (not to exceed 600 mg). The recommended Gleevec dose is 260 mg/m<sup>2</sup>/day for children with Ph+ chronic phase CML recurrent after stem cell transplant or who are resistant to interferon-alpha therapy.

### **2.3 Ph+ ALL**

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

### **2.4 MDS/MPD**

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

### **2.5 ASM**

The recommended dose of Gleevec is 400 mg/day for adult patients with ASM without the D816V c-Kit mutation. If c-Kit mutational status is not known or unavailable, treatment with Gleevec 400 mg/day may be considered for patients with ASM not responding satisfactorily to other therapies. For patients with ASM associated with eosinophilia, a clonal hematological disease related to the fusion kinase FIP1L1-PDGFR $\alpha$ , a starting dose of 100 mg/day is recommended. Dose increase from 100 mg to 400 mg for these patients may be considered in the absence of adverse drug reactions if assessments demonstrate an insufficient response to therapy.

### **2.6 HES/CEL**

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

### **2.7 DFSP**

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

### **2.8 GIST**

The recommended dose of Gleevec is 400 mg/day for adult patients with unresectable and/or metastatic, malignant GIST. A dose increase up to 800 mg daily (given as 400 mg twice daily) may be considered, as clinically indicated, in patients showing clear signs or symptoms of disease progression at a lower dose and in the absence of severe adverse drug reactions.

The recommended dose of Gleevec is 400 mg/day for the adjuvant treatment of adult patients following complete gross resection of GIST. In the clinical study, Gleevec was administered for one year. The optimal treatment duration with Gleevec is not known.

## 2.9 Dose Modification Guidelines

**Concomitant Strong CYP3A4 inducers:** The use of concomitant strong CYP3A4 inducers should be avoided (e.g., dexamethasone, phenytoin, carbamazepine, rifampin, rifabutin, rifampacin, phenobarbital). If patients must be co-administered a strong CYP3A4 inducer, based on pharmacokinetic studies, the dosage of Gleevec should be increased by at least 50%, and clinical response should be carefully monitored [see *Drug Interactions (7.1)*].

**Hepatic Impairment:** Patients with mild and moderate hepatic impairment do not require a dose adjustment and should be treated per the recommended dose. A 25% decrease in the recommended dose should be used for patients with severe hepatic impairment [see *Use in Specific Populations (8.6)*].

**Renal Impairment:** Patients with moderate renal impairment (CrCL = 20-39 mL/min) should receive a 50% decrease in the recommended starting dose and future doses can be increased as tolerated. Doses greater than 600 mg are not recommended in patients with mild renal impairment (CrCL = 40-59 mL/min). For patients with moderate renal impairment doses greater than 400 mg are not recommended.

Imatinib should be used with caution in patients with severe renal impairment. A dose of 100 mg/day was tolerated in two patients with severe renal impairment. [See *Use in Specific Populations (8.7)*]

## 2.10 Dose Adjustment for Hepatotoxicity and Non-Hematologic Adverse Reactions

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

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

## 2.11 Dose Adjustment for Hematologic Adverse Reactions

Dose reduction or treatment interruptions for severe neutropenia and thrombocytopenia are recommended as indicated in Table 1.

**Table 1 Dose Adjustments for Neutropenia and Thrombocytopenia**

ASM associated with eosinophilia (starting dose 100 mg)	ANC <1.0 x 10 <sup>9</sup> /L and/or platelets <50 x 10 <sup>9</sup> /L	1. Stop Gleevec until ANC ≥1.5 x 10 <sup>9</sup> /L and platelets ≥75 x 10 <sup>9</sup> /L 2. Resume treatment with Gleevec at previous dose (i.e., dose before severe adverse reaction)
HES/CEL with FIP1L1-PDGFR $\alpha$ fusion kinase (starting dose 100 mg)	ANC <1.0 x 10 <sup>9</sup> /L and/or platelets <50 x 10 <sup>9</sup> /L	1. Stop Gleevec until ANC ≥1.5 x 10 <sup>9</sup> /L and platelets ≥75 x 10 <sup>9</sup> /L 2. Resume treatment with Gleevec at previous dose (i.e., dose before severe adverse reaction)
Chronic Phase CML (starting dose 400 mg)	ANC <1.0 x 10 <sup>9</sup> /L and/or platelets <50 x 10 <sup>9</sup> /L	1. Stop Gleevec until ANC ≥1.5 x 10 <sup>9</sup> /L and platelets ≥75 x 10 <sup>9</sup> /L 2. Resume treatment with Gleevec at the original starting dose of 400 mg
MDS/MPD, ASM and HES/CEL (starting dose 400 mg)		3. If recurrence of ANC <1.0 x 10 <sup>9</sup> /L and/or platelets <50 x 10 <sup>9</sup> /L, repeat step 1 and resume Gleevec at a reduced dose of 300 mg
GIST (starting dose 400 mg)		
Ph+ CML : Accelerated Phase and	ANC <0.5 x 10 <sup>9</sup> /L	1. Check if cytopenia is related to leukemia (marrow

# Explore Litigation Insights

Docket Alarm provides insights to develop a more informed litigation strategy and the peace of mind of knowing you're on top of things.

## Real-Time Litigation Alerts



Keep your litigation team up-to-date with **real-time alerts** and advanced team management tools built for the enterprise, all while greatly reducing PACER spend.

Our comprehensive service means we can handle Federal, State, and Administrative courts across the country.

## Advanced Docket Research



With over 230 million records, Docket Alarm's cloud-native docket research platform finds what other services can't. Coverage includes Federal, State, plus PTAB, TTAB, ITC and NLRB decisions, all in one place.

Identify arguments that have been successful in the past with full text, pinpoint searching. Link to case law cited within any court document via Fastcase.

## Analytics At Your Fingertips



Learn what happened the last time a particular judge, opposing counsel or company faced cases similar to yours.

Advanced out-of-the-box PTAB and TTAB analytics are always at your fingertips.

## API

Docket Alarm offers a powerful API (application programming interface) to developers that want to integrate case filings into their apps.

## LAW FIRMS

Build custom dashboards for your attorneys and clients with live data direct from the court.

Automate many repetitive legal tasks like conflict checks, document management, and marketing.

## FINANCIAL INSTITUTIONS

Litigation and bankruptcy checks for companies and debtors.

## E-DISCOVERY AND LEGAL VENDORS

Sync your system to PACER to automate legal marketing.