**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**

**----------INDICATIONS AND USAGE----------**
Gleevec is a kinase inhibitor indicated for the treatment of:

- Newly diagnosed adult and pediatric patients with Philadelphia chromosome positive chronic myeloid leukemia (Ph+ CML) in chronic phase. (1.1)
- 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)
- Adult patients with relapsed or refractory Philadelphia chromosome positive acute lymphoblastic leukemia (Ph+ ALL). (1.3)
- Pediatric patients with newly diagnosed Philadelphia chromosome positive acute lymphoblastic leukemia (Ph+ ALL) in combination with chemotherapy. (1.4)
- Adult patients with myelodysplastic/myeloproliferative diseases (MDS/MPD) associated with platelet-derived growth factor receptor (PDGFR) 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-PDGFRα fusion kinase (mutational analysis or fluorescence in situ hybridization [FISH] demonstration of CHIC2 allele deletion) and for patients with HES and/or CEL who are FIP1L1-PDGFRα 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 (2.2): 400 mg/day
- Adults with Ph+ CML AP or BC (2.2): 600 mg/day
- Pediatrics with Ph+ CML CP (2.3): 340 mg/m$^2$/day
- Adults with Ph+ ALL (2.4): 600 mg/day
- Pediatrics with Ph+ ALL (2.5): 340 mg/m$^2$/day
- Adults with MDS/MPD (2.6): 400 mg/day
- Adults with ASM (2.7): 100 mg/day or 400 mg/day
- Adults with HES/CEL (2.8): 100 mg/day or 400 mg/day
- Adults with DFSP (2.9): 800 mg/day
- Adults with metastatic and/or unresectable GIST (2.10): 400 mg/day
- Adjuvant treatment of adults with GIST (2.11): 400 mg/day
- Patients with mild to moderate hepatic impairment (2.12): 400 mg/day
- Patients with severe hepatic impairment (2.12): 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)
- Cytopenias, particularly anemia, neutropenia, and thrombocytopenia, have occurred. Manage with dose reduction, dose interruption, or 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. Monitor and treat patients with cardiac disease or risk factors for cardiac failure. (5.3)
- Severe hepatotoxicity, including fatalities 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 (GI) 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)
- Fetal harm can occur when administered to a pregnant woman. Apprise women of the potential harm to the fetus, and to avoid pregnancy when taking Gleevec. (5.10, 8.1)
- Growth retardation occurring in children and pre-adolescents receiving Gleevec has been reported. Close monitoring of growth in children under Gleevec treatment is recommended. (5.11, 6.2)
- Tumor Lysis Syndrome. Close monitoring is recommended. (5.12)
- Reports of motor vehicle accidents have been received in patients receiving Gleevec. Caution patients about driving a car or operating machinery. (5.13)
- Renal Toxicity. A decline in renal function may occur in patients receiving Gleevec. Evaluate renal function at baseline and during therapy, with attention to risk factors for renal dysfunction. (5.14)

**----------ADVERSE REACTIONS----------**
The most frequently reported adverse reactions (greater than or equal to 30%) were edema, nausea, vomiting, muscle cramps, musculoskeletal pain, diarrhea, rash, fatigue, and abdominal pain. (6.1)

**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.**

**----------DRUG INTERACTIONS----------**

- CYP3A4 inducers may decrease Gleevec $C_{max}$ and area under curve (AUC). (2.12, 7.1, 12.3)
- CYP3A4 inhibitors may increase Gleevec $C_{max}$ and AUC. (7.2, 12.3)
- Gleevec is an inhibitor of CYP3A4 and CYP2D6 which may increase the $C_{max}$ and AUC of other drugs. (7.3, 7.4, 12.3)
- Patients who require anticoagulation should receive low-molecular weight or standard heparin and not warfarin. (7.3)

**See 17 for PATIENT COUNSELING INFORMATION.**

**Revised: 3/2022**

**FULL PRESCRIBING INFORMATION: CONTENTS***



*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 and pediatric patients with Philadelphia chromosome positive chronic myeloid leukemia (Ph+ CML) 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 Adult Patients With Ph+ Acute Lymphoblastic Leukemia (ALL)

Adult patients with relapsed or refractory Philadelphia chromosome positive acute lymphoblastic leukemia (Ph+ ALL).

#### 1.4 Pediatric Patients With Ph+ Acute Lymphoblastic Leukemia (ALL)

Pediatric patients with newly diagnosed Philadelphia chromosome positive acute lymphoblastic leukemia (Ph+ ALL) in combination with chemotherapy.

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

Adult patients with myelodysplastic/myeloproliferative diseases associated with platelet-derived growth factor receptor (PDGFR) 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-PDGFRα fusion kinase (mutational analysis or fluorescence in situ hybridization [FISH] demonstration of CHIC2 allele deletion) and for patients with HES and/or CEL who are FIP1L1-PDGFRα 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

#### 2.1 Drug Administration

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.

For patients unable to swallow the film-coated tablets, the tablets may be dispersed in a glass of water or apple juice. The required number of tablets should be placed in the appropriate volume of beverage (approximately 50 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.

### 2.2 Adult Patients With Ph+ CML CP, AP, or 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 to 12 months of treatment, or loss of a previously achieved hematologic or cytogenetic response.

### 2.3 Pediatric Patients With Ph+ CML CP

The recommended dose of Gleevec for children with newly diagnosed Ph+ CML is 340 mg/m$^2$/day (not to exceed 600 mg). Gleevec treatment can be given as a once daily dose or the daily dose may be split into two–one portion dosed in the morning and one portion in the evening. There is no experience with Gleevec treatment in children under 1 year of age.

### 2.4 Adult Patients With Ph+ ALL

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

### 2.5 Pediatric Patients With Ph+ ALL

The recommended dose of Gleevec to be given in combination with chemotherapy to children with newly diagnosed Ph+ ALL is 340 mg/m$^2$/day (not to exceed 600 mg). Gleevec treatment can be given as a once daily dose.

### 2.6 Adult Patients With MDS/MPD

Determine PDGFRb gene rearrangements status prior to initiating treatment.

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

### 2.7 Adult Patients With ASM

Determine D816V c-Kit mutation status prior to initiating treatment.

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-PDGFRα, 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.

### 2.8 Adult Patients With HES/CEL

The recommended dose of Gleevec is 400 mg/day for adult patients with HES/CEL. For HES/CEL patients with demonstrated FIP1L1-PDGFRα 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.

### 2.9 Adult Patients With DFSP

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

### 2.10 Adult Patients With Metastatic and/or Unresectable 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.

### 2.11 Adult Patients With Adjuvant GIST

The recommended dose of Gleevec is 400 mg/day for the adjuvant treatment of adult patients following complete gross resection of GIST. In clinical trials, one year of Gleevec and three years of Gleevec were studied. In the patient population defined in Study 2, three years of Gleevec is recommended *[see Clinical Studies (14.8)]*. The optimal treatment duration

### 2.12 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 coadministered 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 (creatinine clearance [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 Warnings and Precautions (5.3), Use in Specific Populations (8.7)]*.

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

If elevations in bilirubin greater than 3 times the institutional upper limit of normal (IULN) or in liver transaminases greater than 5 times the IULN occur, Gleevec should be withheld until bilirubin levels have returned to a less than 1.5 times the IULN and transaminase levels to less than 2.5 times the 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$^2$/day to 260 mg/m$^2$/day.

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.

### 2.14 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 less than 1.0 x 10$^9$/L and/or platelets less than 50 x 10$^9$/L | 1. Stop Gleevec until ANC greater than or equal to 1.5 x 10$^9$/L and platelets greater than or equal to 75 x 10$^9$/L<br>2. Resume treatment with Gleevec at previous dose (i.e., dose before severe adverse reaction) |
| HES/CEL with FIP1L1-PDGFRα fusion kinase (starting dose 100 mg) | ANC less than 1.0 x 10$^9$/L and/or platelets less than 50 x 10$^9$/L | 1. Stop Gleevec until ANC greater than or equal to 1.5 x 10$^9$/L and platelets greater than or equal to 75 x 10$^9$/L<br>2. Resume treatment with Gleevec at previous dose (i.e., dose before severe adverse reaction) |
| Chronic Phase CML (starting dose 400 mg)<br><br>MDS/MPD, ASM and HES/CEL (starting dose 400 mg)<br><br>GIST (starting dose 400 mg) | ANC less than 1.0 x 10$^9$/L and/or platelets less than 50 x 10$^9$/L | 1. Stop Gleevec until ANC greater than or equal to 1.5 x 10$^9$/L and platelets greater than or equal to 75 x 10$^9$/L<br>2. Resume treatment with Gleevec at the original starting dose of 400 mg<br>3. If recurrence of ANC less than 1.0 x 10$^9$/L and/or platelets less than 50 x 10$^9$/L, repeat step 1 and resume Gleevec at a reduced dose of 300 mg |

DOCKET ALARM

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