

# About Gleevec

Gleevec<sup>®</sup> (imatinib mesylate)<sup>\*</sup> tablets have fundamentally changed how some patients with certain types of chronic myeloid leukemia (CML) are treated, and the way researchers develop new cancer treatments. Gleevec broke new ground by becoming one of the first targeted cancer drugs to be developed using "rational drug design," a process based on an understanding of how cancer cells work.

- Gleevec is one of the first drugs to validate rational drug design based on an understanding of how certain cancer cells work.
- Gleevec is a signal transduction inhibitor, which targets the pathways that signal the growth of certain tumor cells.
  - Gleevec has been shown to inhibit the function of certain proteins called tyrosine kinases in Philadelphia-chromosome positive (Ph+) chronic myeloid leukemia (CML).
  - In Kit-positive gastrointestinal stromal tumors (GISTs), Gleevec inhibits the activity of Kit (CD117), one of the tyrosine kinases that drive the growth and division of most GISTs.
  - Researchers have found that Gleevec also inhibits other receptor tyrosine kinases — including the platelet-derived growth factor tyrosine kinase (PDGFR) — which have been shown to be activated in disease pathways that underlie a number of rare hematologic diseases, as well as some solid tumors.

## Gleevec in Ph+ CML

Gleevec<sup>®</sup> (imatinib mesylate) tablets are indicated for the treatment of newly diagnosed adult and pediatric patients with Ph+ CML in chronic phase. Follow-up is limited. Gleevec is also indicated for the treatment of patients with Ph+ CML in blast crisis, in accelerated phase, or in chronic phase after failure of interferon-alpha (INF-a) therapy. Gleevec is also indicated for the treatment of pediatric patients with Ph+ CML in chronic phase whose disease has recurred after stem cell transplant or who are resistant to treatment with interferon-alpha (INF-a). There are no controlled trials in pediatric patients demonstrating a clinical benefit, such as improvement in disease-related symptoms or increased survival.

In June 1998, Phase I clinical trials of Gleevec were initiated in patients with Ph+ CML in chronic phase after failure of INF-a therapy. Since then Gleevec has become the most commonly prescribed drug therapy for Ph+ CML patients, with now more than 200,000 patients on the treatment, producing responses at all stages of the disease.

Conventional drug treatments (e.g., INF-a) had shown some efficacy in patients with early stage CML, but have not shown efficacy in patients with advanced disease.

## Five-Year Data in Ph+ CML<sup>†</sup>

Recent data showed that the five-year overall survival of newly-diagnosed Ph+ CML chronic-phase adult patients who received Gleevec as initial therapy is higher—estimated at 95% when

<sup>\*</sup> Known as Glivec<sup>®</sup> (imatinib) outside the U.S., Canada and Israel

<sup>†</sup> These data are currently under review by the U.S. FDA. The inclusion of this data in the Gleevec label is pending the outcome of this review.

excluding deaths from causes unrelated to CML or prior transplantation—than that in any previously published prospective study of the treatment of Ph+ CML, a disease with limited survival options before the approval of Gleevec.<sup>1</sup>

Results of the International Randomized Interferon versus STI571 (IRIS) study—the largest clinical trial ever for this patient population—showed that responses to therapy with Gleevec continued to increase substantially over five years, while the estimated yearly risk of progression to advanced disease declined to 0.6% in the fifth year.<sup>1</sup>

The estimated overall survival rate for patients receiving Gleevec was 89% (range 86% to 92%) when considering deaths from all causes. However, when deaths from causes unrelated to CML or prior transplantation are excluded, the overall survival rate was 95% at 60 months.<sup>1</sup>

Gleevec has continued to be generally well-tolerated as initial drug therapy for Ph+ CML in chronic phase at the five-year follow-up. With a median follow up of 60 months, the adverse events were similar to the previously reported profile. Newly occurring or worsening grade 3 or 4 hematologic or biochemical adverse events were infrequent after two and four years of therapy.

### **IRIS study details**

The International Randomized Interferon versus STI571 (IRIS) study is an open-label Phase III clinical trial enrolling 1,106 newly diagnosed patients with Ph+ CML in chronic phase in 177 centers across 16 countries. There are two arms to the study: one group of patients receiving Gleevec 400 mg per day and another receiving a target dose of interferon (IFN) of 5 MIU/m<sup>2</sup>/day in combination with Ara-C 20 mg/m<sup>2</sup>/day for 10 days each month. Because of tolerability reasons, lack of response, or loss of response, 65% of patients in the IFN/Ara-C arm crossed over to the Gleevec arm, whereas only 3% of patients in the Gleevec arm crossed over to the IFN/Ara-C arm.<sup>1</sup>

Cumulative best responses to Gleevec treatment improved dramatically between the first and fifth years of treatment. Over this period, major cytogenetic responses rose from 85% to 92% and complete cytogenetic responses rose from 69% to 87%. Complete hematologic responses rose from 96% to 98%. In a complete hematologic response, the patient's blood cell counts return to normal. Cytogenetic response refers to the disappearance or reduction of the number of Ph+ cells detectable by standard lab methods.<sup>1</sup>

### **Gleevec in Gastrointestinal Stromal Tumors**

Gleevec tablets are indicated for the treatment of patients with Kit (CD117)-positive unresectable and/or metastatic malignant gastrointestinal stromal tumors. The effectiveness of Gleevec in GIST is based on objective response rate. There are no controlled trials demonstrating a clinical benefit, such as improvement in disease-related symptoms or increased survival.

#### *Epidemiology, Diagnosis and Treatment of GIST:*

- The introduction of Gleevec has dramatically affected the management of patients diagnosed with GIST leading to advances in diagnosis and classification methods. These recent advances have demonstrated that GISTs may be more prevalent than previously believed.<sup>2</sup> Based on a Swedish epidemiology study, the estimated prevalence of GIST in the U.S. is 9,000 (31 per million, high-risk/metastatic/malignant GIST).<sup>3</sup>
- Prior to Gleevec, if surgery was not effective or possible, other options for treating GIST were limited and offered little hope for recovery.<sup>4</sup> Today, Gleevec has been confirmed as a highly

effective therapy for patients with Kit (CD117)-positive metastatic or unresectable GIST. Gleevec has fundamentally changed the natural history of this disease, with a median overall survival of 58 months (4.8 years)<sup>5</sup> versus an historical survival of approximately 15 months with chemotherapy.

- The majority of patients derive benefit from Gleevec treatment, and responses in general are usually of lasting duration.<sup>4</sup>
- The median onset of response to Gleevec was found to be relatively fast (12 weeks) for most patients; however, responses have been achieved between 3 and 98 weeks. In particular, late responses were often seen in patients with initial stable disease.<sup>4</sup> The authors of the largest GIST study to date advised against interrupting or discontinuing Gleevec therapy in patients with stable disease (e.g., “non-responding patients”), in addition to those with partial or complete responses.<sup>4\*\*</sup>

As additional data about Gleevec become available, more is being learned about the optimal management of GIST patients.

- Studies are under way to investigate treatment with Gleevec at a higher dose for patients with advanced GIST.
  - In a recent study, patients with widespread metastatic disease taking an initial investigational 800 mg daily dose of Gleevec had significantly longer progression-free survival compared to the patients taking 400 mg daily dose<sup>6</sup>.
  - In the same study, patients whose tumors expressed a certain mutation called exon 9 had significantly superior progression-free survival ( $p=0.0013$ ) when administered Gleevec at 800 mg/day. Those patients had a 61% reduction in their relative risk of progression compared to patients with the exon 9 mutation who received 400 mg/day.<sup>7</sup>
- In addition, there are studies under way investigating the use of Gleevec in less advanced disease and in association with standard surgical treatment of GIST focusing on:
  - Preoperative treatment that may shrink tumors enough to facilitate surgery (resection) of tumors that previously would not be completely operable (neoadjuvant).
  - Postoperative treatment, soon after surgery, that may prevent or delay recurrence of GIST (adjuvant treatment).
    - An interim analysis of a recent study involving more than 600 adult patients sponsored by the National Cancer Institute (NCI), which is part of the US National Institutes of Health (NIH), showed participants with Kit-positive GIST treated with Gleevec following surgery were significantly less likely to experience a return of their cancer compared to those not taking this innovative therapy.<sup>8</sup>
    - This interim analysis showed no recurrence of cancer in approximately 97% of patients given Gleevec for a year after surgery to remove tumors, compared to approximately 83% of those who underwent surgery but received a placebo. The investigators made these results public earlier than scheduled because the study had met its primary endpoint in terms of the rate of recurrence-free survival.<sup>8</sup>
    - These data are investigational and not included in the current Gleevec label. Regulatory submissions are being planned for use of Gleevec as adjuvant therapy in GIST patients following surgery to remove primary tumor(s).

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\*\* This recommendation is not in the Gleevec U.S. label; further studies are ongoing.

### **Gleevec in Rare Diseases:**

Gleevec is also approved in the U.S. for the treatment of adult patients with unresectable, recurrent and/or metastatic dermatofibrosarcoma protuberans (DFSP), relapsed or refractory Philadelphia chromosome-positive acute lymphoblastic leukemia (Ph+ ALL), certain forms of myelodysplastic/myeloproliferative diseases (MDS/MPD), hypereosinophilic syndrome and/or chronic eosinophilic leukemia (HES/CEL) and aggressive systemic mastocytosis (ASM).

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Gleevec is also indicated for the treatment of: adult patients with relapsed or refractory Ph+ acute lymphoblastic leukemia (Ph+ ALL); adult patients with myelodysplastic/myeloproliferative diseases (MDS/MPD) associated with PDGFR (platelet-derived growth factor receptor) gene rearrangements; adult patients with aggressive systemic mastocytosis (ASM) without the D816V c-Kit mutation or with c-Kit mutational status unknown; adult patients with hypereosinophilic syndrome (HES) and/or chronic eosinophilic leukemia (CEL) who have the FIP1L1-PDGFR fusion kinase (mutational analysis or FISH demonstration of CHIC2 allele deletion) and for patients with HES and/or CEL who are FIP1L1-PDGFR fusion kinase negative or unknown; and for adult patients with unresectable, recurrent and/or metastatic dermatofibrosarcoma protuberans (DFSP).

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

### **Important Safety Information<sup>9</sup>**

In adult Ph+ CML patients, severe (NCI Grades 3/4) lab abnormalities—including neutropenia (3%–48%), anemia (<1%–42%), thrombocytopenia (<1%–33%), and hepatotoxicity (3%–6%)—and severe adverse experiences (NCI Grades 3/4), including severe fluid retention (eg, pleural effusion, pulmonary edema, and ascites) and superficial edema (1.8%–11%), hemorrhage (1%–19%), and musculoskeletal pain (2%–9%) were reported among patients receiving Gleevec.\* Severe fluid retention appears to be dose related, was more common in the advanced phase studies (where the dosage was 600 mg/day), and is more common in the elderly.

Although most pediatric Ph+ CML patients experienced adverse events at some time during the study, the incidence of Grades 3/4 adverse events was low and included neutropenia, thrombocytopenia and anemia, generally within the first several months of therapy.

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\* Numbers indicate the range of percentages in 4 studies among adult patients with Ph+ CML in blast crisis, accelerated phase, and chronic phase.

In HES/CEL patients, instances of Grade 3 leukopenia, neutropenia, lymphopenia, and anemia were reported.

In patients with HES and cardiac involvement, cases of cardiogenic shock/left ventricular dysfunction have been associated with the initiation of imatinib therapy. The condition was reported to be reversible with the administration of systemic steroids, circulatory support measures, and temporarily withholding imatinib. MDS/MPD disease and systemic mastocytosis may be associated with high eosinophil levels. Performance of an echocardiogram and determination of serum troponin should therefore be considered in patients with HES/CEL, and in patients with MDS/MPD or ASM associated with high eosinophil levels. If either is abnormal, the prophylactic use of systemic steroids (1-2 mg/kg) for 1-2 weeks concomitantly with imatinib should be considered at the initiation of therapy.

For DFSP, severe (NCI Grades 3/4) lab abnormalities included anemia (17%), thrombocytopenia (17%), neutropenia (8%), and increased creatinine (8%).

In GIST, severe (NCI Grades 3/4) lab abnormalities (400 mg/day; 600 mg/day)—including neutropenia (10%; 11%), anemia (3%; 9%), thrombocytopenia (0%; 1%), and hepatotoxicity (6%; 8%)—and severe adverse experiences (NCI Grades 3/4), including severe fluid retention (eg, pleural effusion or ascites; 3%; 8%) and superficial edema (6%; 5%), hemorrhage (6%; 11%), abdominal pain (11%; 4%), nausea (6%; 4%), diarrhea (3%; 7%), and musculoskeletal pain (6%; 1%) were reported among patients receiving Gleevec.

Some GIST patients (5%) were reported to have severe GI bleeds and/or intratumoral bleeds. GI tumor sites may have been the source of GI bleeds.

Patients should be weighed and monitored regularly for signs and symptoms of edema, which can be serious or life-threatening. There have also been reports, including fatalities, of cardiac tamponade, cerebral edema, increased intracranial pressure, papilledema, and gastrointestinal (GI) perforation.

Severe congestive heart failure and left ventricular dysfunction have occasionally been reported. Most of the patients with reported cardiac events have had other comorbidities and risk factors, including advanced age and previous medical history of cardiac disease. Patients with cardiac disease or risk factors for cardiac failure should be monitored carefully, and any patient with signs or symptoms consistent with cardiac failure should be evaluated and treated.

Bullous dermatologic reactions (eg, erythema multiforme and Stevens-Johnson syndrome) have also been reported. In some cases, the reaction recurred upon rechallenge. Several postmarketing reports describe patients able to tolerate the reintroduction of Gleevec at a lower dose with or without concomitant corticosteroids or antihistamines following resolution or improvement of the bullous reaction.

Dose adjustments may be necessary due to hepatotoxicity, other nonhematologic adverse events, or hematologic adverse events. Therapy with Gleevec was discontinued for adverse events in 3% to 5% of adult patients with Ph+ CML or Kit-positive GIST. None of the 5 patients in the ASM study discontinued Gleevec due to drug-related events or abnormal laboratory values.

Patients with severe hepatic impairment should be treated at a starting dose of 300 mg/day and should be closely monitored.

Gleevec is metabolized by the CYP3A4 isoenzyme and is an inhibitor of CYP3A4, CYP2D6, and CYP2C9. Dosage of Gleevec should increase by at least 50%, and clinical response should be carefully monitored, in patients receiving Gleevec with a potent CYP3A4 inducer such as rifampin or phenytoin. Examples of commonly used drugs that may significantly interact with Gleevec include acetaminophen, warfarin, erythromycin, and phenytoin. (Please see full Prescribing Information for other potential drug interactions).

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

Use of Gleevec tablets is contraindicated in patients with hypersensitivity to imatinib or to any other component of Gleevec tablets.

Women of childbearing potential should be advised to avoid becoming pregnant while taking Gleevec tablets and should be advised to avoid breast-feeding while taking Gleevec tablets because of the potential for serious adverse reactions in nursing infants.

#### **Common Side Effects of Gleevec Tablets**

The majority of adult Ph+ CML patients who received Gleevec in clinical studies experienced adverse events at some time, but most were mild to moderate in severity. The most frequently reported adverse events (all Grades) were superficial edema (58%–74%), nausea (47%–73%), muscle cramps (28%–62%), vomiting (21%–58%), diarrhea (39%–57%), musculoskeletal pain (38%–49%), and rash and related terms (36%–47%).\*†

The overall safety profile of Ph+ CML pediatric patients treated with Gleevec in 93 children studied was similar to that found in studies with adult patients, except that musculoskeletal pain was less frequent (20.5%) and peripheral edema was not reported. Nausea and vomiting were the most commonly reported individual adverse events with an incidence similar to that seen in adult patients.

The adverse reactions and safety profile for Ph+ ALL, MDS/MPD, ASM and HES/CEL were generally similar to the safety profile for Ph+ CML.

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

Frequently reported adverse events (all Grades) in the seven MDS/MPD patients assessed were nausea (57%); diarrhea and muscle cramps (43% each); anemia, fatigue, arthralgia, and periorbital edema (29% each).

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\* Numbers indicate the range of percentages in 4 studies among adult patients with Ph+ CML in blast crisis, accelerated phase, and chronic phase.

† For more detailed study information, please see full Prescribing Information.

All ASM patients experienced at least one adverse event at some time. The most frequently reported adverse events were diarrhea, nausea, ascites, muscle cramps, dyspnea, fatigue, peripheral edema, anemia, pruritis, rash and lower respiratory tract infection.

All HES/CEL patients experienced at least one adverse event, the most common being gastrointestinal, cutaneous and musculoskeletal disorders. Hematological abnormalities were also frequent, with instances of Grade 3 leukopenia, neutropenia, lymphopenia, and anemia.

Frequently reported adverse events (all Grades) in the 12 DFSP patients assessed included nausea and fatigue (42% each); periorbital, peripheral and eye edema (33% each); diarrhea, vomiting, rash, lacrimation increased, and anemia (25% each); face edema, pyrexia, exertional dyspnea, rhinitis and anorexia (17% each).

The majority of patients who received Gleevec in the GIST study experienced adverse events at some time. Most adverse events were mild to moderate in severity. The most frequently reported adverse events (400 mg/day; 600 mg/day) (all Grades) were superficial edema (81%; 77%) nausea (63%; 74%), muscle cramps (47%; 58%), diarrhea (59%; 70%), fatigue (48%; 53%), abdominal pain (40%; 37%), rash and related terms (38%; 53%) vomiting (38%; 35%) musculoskeletal pain (37%; 30%), and hemorrhage (26%; 34%).\*

Supportive care may help management of some mild to moderate adverse events so that the prescribed dose can be maintained whenever possible. However, in some cases, either a dose reduction or interruption of treatment with Gleevec may be necessary.

Gleevec tablets should be taken with food and a large glass of water to minimize GI irritation. Gleevec tablets should not be taken with grapefruit juice.

## References:

<sup>1</sup> Druker, B. et al. Five-Year Follow-up of Patients Receiving Imatinib for Chronic Myeloid Leukemia. *N Engl J Med* 2006;355:2408-17.

<sup>2</sup> Kindblom, LG. Gastrointestinal stromal tumors: current management and future challenges. ASCO Virtual Meeting. 2003. Available at: <http://www.asco.org>.

<sup>3</sup> Kindblom L-G, Meis-Kindblom J, Bumming P, et al. Incidence, prevalence, phenotype and biologic spectrum of gastrointestinal stromal cell tumours (GIST) - a population study based on 600 cases. *Ann Oncol.* 2002; 13 (suppl 5):157. Abstract 5770

<sup>4</sup> Demetri GD, et al. NCCN task force report: optimal management of patients with gastrointestinal stromal tumor (GIST)—expansion and update of NCCN clinical practice guidelines. *J Natl Compr Cancer Network*,2004;2(suppl 1):S1-S26.

<sup>5</sup> Blanke CD, Joensuu H, Demetri GD et al. Outcome of Advanced Gastrointestinal Stromal Tumor (GIST) Patients Treated With Imatinib Mesylate: Four-Year Follow-Up of a Phase II Randomized Trial. ASCO GI Symposium Meeting. 2006

<sup>6</sup> Verweij J, et al. Progression-free survival in gastrointestinal stromal tumours with high-dose imatinib: randomised trial. *Lancet.* 2004 Sep 25;364(9440):1127-34.

<sup>7</sup> M Debiec-Rychter, R Sciot, A Le Cesne et al, on behalf of the EORTC Soft Tissue and Bone Sarcoma Group, The Italian Sarcoma Group and the Australasian GastroIntestinal Trials Group. Kit mutations and dose selection for imatinib in patients with advanced gastrointestinal stromal tumours. 2006 Apr 16

<sup>8</sup> Z9001: A Phase III Randomized Double-blind Study of Adjuvant STI571 (Gleevec®) Versus Placebo in Patients Following the Resection of Primary Gastrointestinal Stromal Tumor (GIST)

<sup>9</sup> Gleevec® (imatinib mesylate) tablets prescribing information. East Hanover, NJ: Novartis Pharmaceuticals Corporation; Nov 2006.

\* For more detailed study information, please see full Prescribing Information.

**This resource includes information on approved and investigational uses of Gleevec and is intended solely as background information for journalists.**