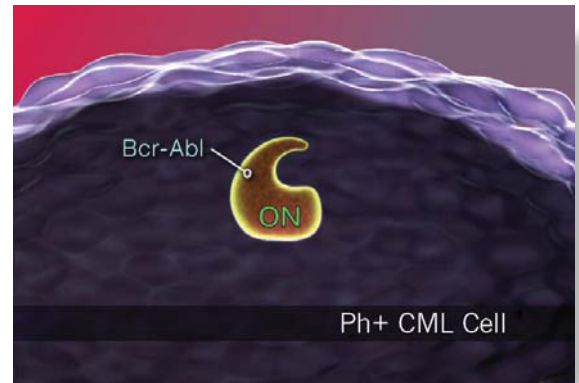


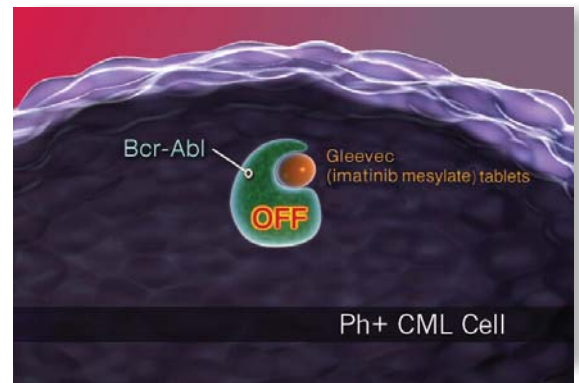
Targeting the Key Cause and Driver of Ph+ CML

Healthy cells make specialized proteins called tyrosine kinases, or TK, which normally turn cell division on and off. The cells of some cancers, like chronic myeloid leukemia (CML), develop a genetic abnormality which results in the production of a malfunctioning TK protein. Bcr-Abl is a malfunctioning TK and the key cause and driver of Philadelphia chromosome-positive CML (or Ph+ CML). Bcr-Abl switches are stuck at the “on” position and tells the body to continue producing white blood cells. These forces drive the Ph+ CML cells to continually divide.

Traditional chemotherapy typically kills dividing cells, good or cancerous. Gleevec® (imatinib mesylate) tablets* is designed to target the Ph+ CML cells. By attaching to Bcr-Abl, Gleevec turns off the switch that signals the body to continue producing white blood cells.



Bcr-Abl switches are stuck at the “on” position.



Gleevec turns off the switch that signals the body to continue producing white blood cells.

* Known as Glivec® (imatinib) outside the U.S., Canada and Israel.

About Gleevec

Gleevec[®] (imatinib mesylate) tablets is indicated for the treatment of newly diagnosed adult patients with Philadelphia chromosome–positive chronic myeloid leukemia (Ph+ CML) in the chronic phase. Follow-up is limited to 5 years. Gleevec is also indicated for the treatment of patients with Ph+ CML in blast crisis (BC), accelerated phase (AP), or in the chronic phase (CP) after failure of interferon-alpha therapy.

Important Safety Information¹

Fetal harm can occur when administered to a pregnant woman; therefore, women of childbearing potential should be advised to not become pregnant while taking Gleevec tablets and to avoid breast-feeding while taking Gleevec tablets because of the potential for serious adverse reactions in nursing infants. Sexually active female patients taking Gleevec should use adequate contraception. If the patient does become pregnant while taking Gleevec, the patient should be advised of the potential hazard to the fetus.

Severe (NCI Grades 3/4) lab abnormalities—including neutropenia (3.6%–48%), anemia (1%–42%), thrombocytopenia (<1%–33%), and hepatotoxicity (approx 5%)—and severe adverse experiences (NCI Grades 3/4), including severe fluid retention (eg, pleural effusion, pulmonary edema, and ascites) and superficial edema (1.3%–11%), hemorrhage (1.8%–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.

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.

Dose adjustments may be necessary due to hepatotoxicity, other nonhematologic adverse reactions, or hematologic adverse reactions. Therapy with Gleevec was discontinued for drug-related adverse reactions in 2.4% to 5% of patients.

A 25% decrease in the recommended dose should be used for patients with severe hepatic impairment.

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.

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

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

lower dose with or without concomitant corticosteroids or antihistamines following resolution or improvement of the bullous reaction.

Consider potential toxicities—specifically liver, kidney, and cardiac toxicity, and immunosuppression from long-term use.

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 ketoconazole, 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 tablet to reduce exposure to iron.

Common Side Effects of Gleevec Tablets

The majority of adult Ph+ CML patients who received Gleevec in clinical studies experienced adverse reactions at some time, but most were mild to moderate in severity. The most frequently reported adverse reactions (all Grades) were superficial edema (60%–74%), nausea (50%–73%), muscle cramps (28%–62%), vomiting (23%–58%), diarrhea (43%–57%), musculoskeletal pain (38%–49%), and rash and related terms (36%–47%).^{*†}

Supportive care may help management of some mild-to-moderate adverse reactions 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 and other foods known to inhibit CYP3A4.

Patients should be informed to take Gleevec exactly as prescribed, not to change their dose or stop taking Gleevec unless they are told to do so by their doctor. If patients miss a dose, they should be advised to take their does as soon as possible unless it is almost time for their next dose, in which case the missed dose should not be taken. A double dose should not be taken to make up for any missed dose.

¹ Gleevec[®] (imatinib mesylate) tablets prescribing information. East Hanover, NJ: Novartis Pharmaceuticals Corporation; Sep 2007.

* 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.