

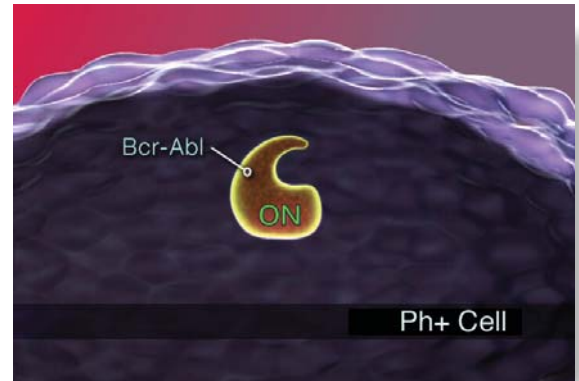
Targeting the Key Cause and Driver of Ph+ CML

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.

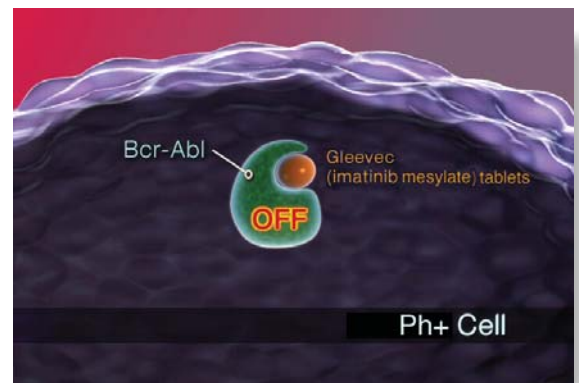
Traditional chemotherapy typically kills dividing cells, good or cancerous. Gleevec® (imatinib mesylate) tablets* is designed to target the Ph+ CML cells. By attaching to Bcr-Abl, Gleevec turns off the switch that signals the body to continue producing white blood cells.

Cancer cells can protect themselves by mutating when challenged. Ongoing studies have shown a small percentage of cases where Ph+ CML cells never respond to, or stop responding to, Gleevec. In addition, a small subset of patients cannot tolerate therapy with Gleevec.

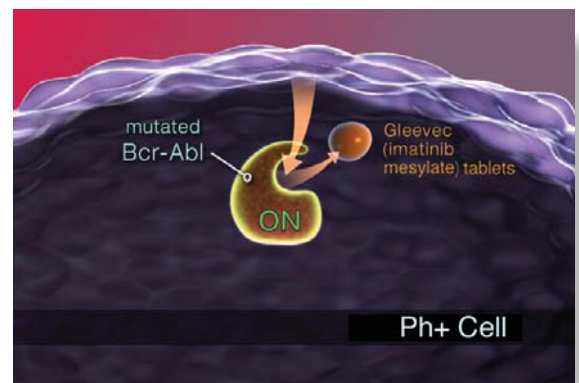
Building on the vast knowledge and experience gained during the development of Gleevec, Novartis has developed Tasigna (nilotinib) capsules, a next generation TK inhibitor. Tasigna was specifically designed to target the Bcr-Abl protein more preferentially than Gleevec without adding new targets. In preclinical studies, the medicine was able to overcome resistance resulting from Bcr-Abl kinase mutations in 32 of 33 cell lines commonly associated with Ph+ CML. Tasigna has been approved for the treatment of chronic phase and accelerated phase Ph+ CML in adult patients resistant to or intolerant to prior therapy that included Gleevec.



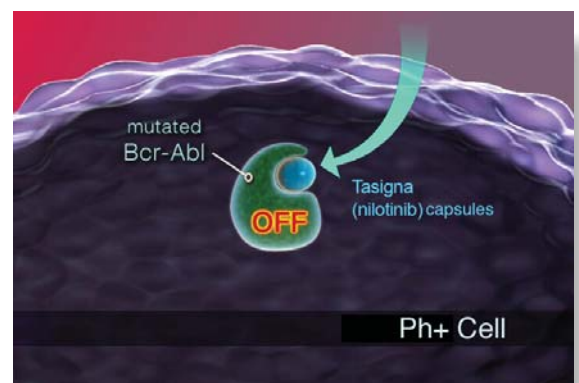
Bcr-Abl switches are stuck at the “on” position.



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



Ph+ cells can protect themselves by mutating.



Tasigna is designed to work where Gleevec does not.

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

About Tasigna

Tasigna[®] (nilotinib) capsules are indicated for the treatment of chronic-phase and accelerated-phase Philadelphia chromosome-positive (Ph+) chronic myelogenous leukemia (CML) in adult patients resistant to or intolerant to prior therapy that included Gleevec[®] (imatinib mesylate) tablets. The effectiveness of Tasigna is based on hematologic and cytogenetic response rates. There are no controlled trials demonstrating a clinical benefit, such as improvement in disease-related symptoms or increased survival.

Tasigna important safety information

Tasigna prolongs the QT interval. Sudden deaths have been reported in patients receiving Tasigna. Tasigna should not be used in patients with hypokalemia (low potassium levels), hypomagnesemia (low magnesium levels), or long QT syndrome. Hypokalemia or hypomagnesemia must be corrected prior to Tasigna administration and should be periodically monitored. Drugs known to prolong the QT interval and strong CYP3A4 inhibitors should be avoided. Patients should avoid food two hours before and one hour after taking dose. Use with caution in patients with hepatic impairment. ECGs should be obtained to monitor the QTc at baseline, seven days after initiation, and periodically thereafter, as well as following any dose adjustments.

Warnings and precautions

Myelosuppression: Associated with neutropenia, thrombocytopenia and anemia. CBC should be done every 2 weeks for the first 2 months, then monthly. Reversible by withholding dose. Dose reduction may be required.

QT Prolongation: Tasigna prolongs the QT interval. Correct hypokalemia or hypomagnesemia prior to administration and monitor periodically. Avoid drugs known to prolong the QT interval and strong CYP3A4 inhibitors. Use caution in patients with hepatic impairment. Obtain ECGs at baseline, seven days after initiation, and periodically thereafter, as well as following any dose adjustments.

Sudden deaths: There were sudden deaths reported in the safety population and the expanded access program. Ventricular repolarization abnormalities may have contributed to their occurrence.

Elevated serum lipase: Caution is recommended in patients with history of pancreatitis. Check serum lipase periodically.

Liver function abnormality: Tasigna may result in elevations in bilirubin, AST/ALT, and alkaline phosphatase. Check hepatic function tests periodically.

Electrolyte abnormalities: Tasigna can cause hypophosphatemia, hypokalemia, hyperkalemia, hypocalcemia, and hyponatremia. Correct electrolyte abnormalities prior to initiating Tasigna and monitor periodically during therapy.

Hepatic impairment: Tasigna has not been investigated in patients with hepatic impairment. Caution is recommended in these patients and QT interval should be monitored closely.

Drug interactions: Avoid concomitant use of strong inhibitors or inducers of CYP3A4. If patients must be co-administered a strong CYP3A4 inhibitor, dose reduction should be considered and the QT interval should be monitored closely.

Food Effects: Food increases blood levels of Tasigna. Avoid food 2 hours before and 1 hour after a dose.

Since the capsules contain lactose, Tasigna is not recommended for patients with rare hereditary problems of galactose intolerance, severe lactase deficiency or of glucose-galactose malabsorption.

Pregnancy: Fetal harm can occur when administered to a pregnant woman. Women should be advised not to become pregnant when taking Tasigna.

Adverse reactions

In chronic-phase CML patients, the most commonly reported drug-related adverse reactions (>10%) were rash, pruritis, nausea, fatigue, headache, constipation, diarrhea and vomiting. The common serious drug-related adverse reactions were thrombocytopenia and neutropenia. In accelerated-phase CML patients, the most commonly reported drug-related adverse reactions (>10%) were rash, pruritis and constipation. The common serious drug-related adverse reactions were thrombocytopenia, neutropenia, pneumonia, febrile neutropenia, leukopenia, intracranial hemorrhage, elevated lipase and pyrexia.

Tasigna may need to be withheld and/or dose reduced for QT interval prolongation, myelosuppression, and certain non-hematologic laboratory abnormalities (e.g., Grade \geq 3 elevated serum lipase or amylase, bilirubin and hepatic transaminases) as well as for other non-hematologic toxicities. Therapy with Tasigna was discontinued for drug-related adverse reactions in 11% and 8% of chronic-phase and accelerated-phase CML patients, respectively.

About Gleevec

Gleevec[®] (imatinib mesylate) tablets are 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.

Gleevec 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 (e.g., 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

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

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 (e.g., 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.

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%).*†

* 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.

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 dose 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.

References:

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