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Novartis Oncology: Commitment to Patients with Ph+ Chronic Myeloid Leukemia

Novartis is fully committed to discovering, developing and producing novel therapies that improve the lives of patients with cancer. The approval of Gleevec® (imatinib mesylate) tablets,* the first molecularly targeted therapy for the treatment of Philadelphia chromosome-positive (Ph+) chronic myeloid leukemia (CML) exemplified this commitment.

In striving toward a comprehensive treatment strategy to best serve patients with Ph+ CML, Novartis scientists applied the principles that drove the discovery of Gleevec to help patients who do not respond, have lost response, or are intolerant to treatment with Gleevec. The result of this research, Tasigna® (nilotinib) capsules is one part of a broad effort by Novartis to continue discovering and developing new compounds with the goal of providing more treatment options for patients with Ph+ CML.

About CML

CML is one of the most common forms of leukemia. It is primarily caused by an *oncogene* – a gene that induces cancer, usually by transforming proteins involved in the control of cell growth or division. In Ph+ CML, the Bcr-Abl oncogene (marked by the Philadelphia chromosome) ultimately produces the proteins responsible for blocking the signal that tells the body to stop producing white blood cells. Moreover, the oncogene can continue to acquire mutations, making some subtypes of Ph+ CML very challenging to treat.

Mortality from CML has declined rapidly since 2001. In the US, the American Cancer Society estimates that 4,500 new cases of CML were diagnosed in 2006, with approximately 600 deaths occurring.¹ This represents nearly a 75% decrease in mortality from 2001, when 4,700 new cases of CML were diagnosed and approximately 2,300 deaths occurred.²

An Ever Advancing Frontier

Gleevec is one of the first oncology drugs that validate rational drug design, which is based on an understanding of how certain cancer cells work. In Ph+ CML, Gleevec inhibits the Bcr-Abl tyrosine kinase, the protein that is the key cause and driver of Ph+ CML. The development and clinical use of Gleevec have significantly enhanced scientific understanding of Ph + CML and improved the treatment of patients with this disease.

Gleevec has a unique five-year record of efficacy and safety. Data from the landmark International Randomized Interferon versus STI571 (IRIS) trial - the largest ever conducted in newly diagnosed chronic-phase adult Ph+ CML patients - demonstrated that nearly 90% of chronic-phase Ph+ CML patients taking Gleevec were alive at five years, with the latest analysis showing less than 5% mortality due to Ph+ CML.³

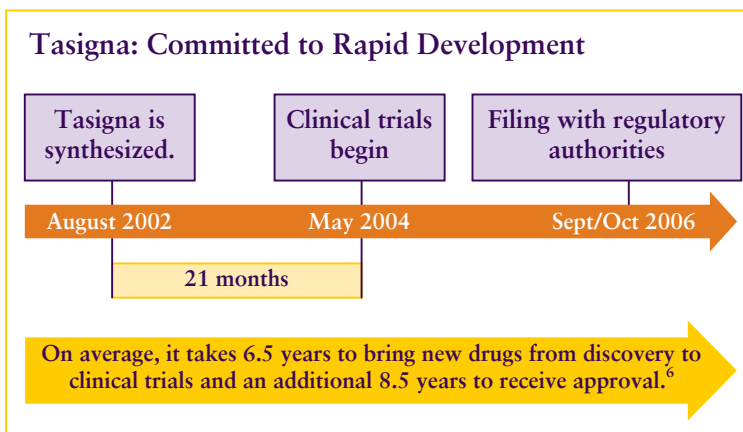
*Known as Glivec® (imatinib) outside the U.S., Canada and Israel

Next-Generation

Despite the success of Gleevec, a small subset of patients develop resistance or cannot tolerate this therapy. Identifying options for these patients is a crucial part of developing a comprehensive treatment strategy. Novartis continued its pioneering work in the field of targeted therapies by developing a next-generation tyrosine kinase inhibitor, Tasigna.

Tasigna was specifically designed to target Bcr-Abl, the key cause and driver of Ph+ CML, more preferentially than Gleevec without adding new targets. In preclinical studies, Tasigna was able to overcome resistance resulting from Bcr-Abl kinase mutations in 32 of 33 cell lines commonly associated with Ph+ CML.⁴ Preliminary data from the pivotal Phase II

clinical trials revealed impressive response rates in Gleevec resistant and intolerant patients treated with Tasigna. Tasigna reduced or eliminated the presence of the abnormal chromosome that causes Ph+ CML in 40% of patients in chronic phase of this disease. Many of the patients involved in the trial were heavily pretreated with other therapies in addition to Gleevec prior to receiving Tasigna.⁵



Access – A Core Principle

Given the unprecedented results of Gleevec in early phase studies, Novartis built an Expanded Access Program (EAP) into the clinical research protocols. Before Gleevec became commercially available, more than 7,300 patients in 37 countries received the drug at no cost through the EAP.

Novartis also introduced the Gleevec International Patient Assistance Program (GIPAP) – one of the most generous and far-reaching international patient assistance programs ever developed for a breakthrough cancer therapy. GIPAP provides Gleevec in accordance with the drug's specific approved use in countries at no cost to qualified patients who are properly diagnosed, not insured, not reimbursed, and have no other financial resource (i.e., who cannot pay for it privately). As of March 2007, Novartis has provided Gleevec through GIPAP to approximately 22,000 patients in more than 80 countries who would not otherwise have access to the drug.

In early 2006, Novartis also launched ENACT (Expanding Nilotinib Access in Clinical Trials), a global program to provide expanded access to the compound prior to approval to eligible adult patients in all phases of Ph+ CML who are either resistant to or intolerant of treatment with Gleevec.

CML Alliance™ – Commitment & Leadership

Novartis recently introduced CML Alliance, a new clinical support program with a key goal: to help optimize outcomes in Ph+ CML patients. This program offers healthcare professionals and patients the latest resources, including patient education, access to standardized molecular testing, access to reimbursement support services and information on clinical trials with investigational agents and existing therapies in CML.

For More Information

Information about Novartis clinical trials for Tasigna, Gleevec and other agents is also available by contacting the Novartis local offices or local call center, which will refer requests to the appropriate clinical team. Physicians can access information at www.amn107.com.

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, pruritus 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 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 Information⁶

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 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

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

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 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:

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- ¹ American Cancer Society Cancer Facts & Figures 2006
 - ² American Cancer Society Cancer Facts & Figures 2001
 - ³ Druker, B. et al. Five-Year Follow-up of Patients Receiving Imatinib for Chronic Myeloid Leukemia. *N Engl J Med* 2006;355:2408-17.
 - ⁴ Manley P, et al. AMN107: Inhibitory profile against wild-type and mutant forms of the bcr-abl tyrosine kinase. Presented at the 2005 American Association for Cancer Research Annual Meeting. Abstract #5985.
 - ⁵ IeCoutre P, et al. A Phase II Study of Nilotinib, A Novel Tyrosine Kinase Inhibitor Administered to Imatinib Resistant and Intolerant Patients With Chronic Myeloid Leukemia (CML) in Chronic Phase (CP). Presented at the 2006 American Society of Hematology Annual Meeting.
 - ⁶ PhRMA (Pharmaceutical Research and Manufacturers of America) ; *2005 Survey: Medicines in Development for Cancer: 59*
 - ⁷ Gleevec® (imatinib mesylate) tablets [prescribing information]. East Hanover, NJ: Novartis Pharmaceuticals Corporation; Nov 2006.
 - ⁶ 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.