

## For Media Use Only

### Tasigna® (nilotinib) capsules

Tasigna® (nilotinib) capsules, a tyrosine kinase inhibitor, is indicated for treatment of chronic phase and accelerated phase Philadelphia chromosome-positive (Ph+) chronic myeloid leukemia (CML) in adult patients resistant or intolerant to prior therapy that included Gleevec (imatinib mesylate) tablets.\*

<b>Tasigna in Ph+ CML</b>	<p>Tasigna was approved in the U.S. in October 2007 for the treatment of chronic phase and accelerated phase Ph+ CML in adult patients resistant or intolerant to prior therapy that included Gleevec.</p> <p>Gleevec, one of the first targeted therapies, works by attaching to a malfunctioning protein known as Bcr-Abl, the key cause and driver of Ph+ CML. Gleevec has a unique five-year record of efficacy and safety. Data from the largest trial 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.<sup>1</sup> However, a small subset of patients develop resistance or cannot tolerate therapy with Gleevec.</p>
<b>Efficacy</b>	<p>Building on the vast experience and knowledge gained with Gleevec, Novartis developed Tasigna. Committed to providing Ph+ CML patients with a new treatment option, Novartis accelerated the clinical development of Tasigna. The compound entered clinical trials just 21 months after discovery and was filed with regulatory authorities within four years. (On average, it takes 6.5 years to bring new drugs from discovery to clinical trials and an additional 8.5 years to receive approval.<sup>2</sup>)</p> <p>Like Gleevec, Tasigna works by attaching to Bcr-Abl. 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.</p> <p>Preliminary data from clinical studies in Ph+ CML revealed impressive response rates in both resistant and intolerant patients treated with Tasigna. Tasigna reduced or eliminated the presence of the abnormal Ph chromosome in patients in the chronic or accelerated phases of the disease. Further exploration of the potential benefits of Tasigna is ongoing.</p>
<b>About CML</b>	<p>Chronic myeloid leukemia, also known as chronic myelogenous leukemia, is a form of cancer in which white blood cells do not mature and become too numerous.</p> <ul style="list-style-type: none"><li>• CML is one of the four most common types of leukemia.</li><li>• The American Cancer Society estimates that 4,570 new cases of CML will be diagnosed and approximately 490 deaths from CML will occur in 2007.<sup>3</sup></li><li>• CML usually affects the middle-age population, and the average age of people with CML is 66.<sup>3</sup></li><li>• About 2% of cases are diagnosed in children.<sup>4</sup></li></ul> <p>In nearly all CML patients (95%-100%), an abnormal chromosome called the Philadelphia (Ph) chromosome can be found.<sup>5</sup> This chromosome leads to the production of a malfunctioning tyrosine kinase (TK), a specialized protein normally responsible for turning cell division on and off. This faulty tyrosine kinase known as Bcr-Abl upsets the normal balance of white blood cell production.</p> <p>Mortality from Ph+ CML has declined rapidly since 2001. In the U.S., the American Cancer Society estimates that 4,500 new cases of CML were diagnosed in 2006, with approximately 600 deaths occurring<sup>6</sup>. 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.<sup>7</sup></p>
<b>Tasigna in Other Diseases</b>	<p>Based on encouraging results of preclinical laboratory studies evaluating Tasigna's activity against the c-Kit protein, which is associated with most gastrointestinal stromal tumors, or GISTs, clinical trials of Tasigna in adult patients with Kit-positive GIST who are resistant or intolerant to Gleevec are underway.</p>

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

---

## For More Information

Information about Novartis clinical trials for Tassigna, 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](http://www.amn107.com).

---

## About Tassigna

Tassigna<sup>®</sup> (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<sup>®</sup> (imatinib mesylate) tablets. The effectiveness of Tassigna 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.

## Tassigna important safety information

Tassigna prolongs the QT interval. Sudden deaths have been reported in patients receiving Tassigna. Tassigna 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 Tassigna 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:** Tassigna 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:** Tassigna may result in elevations in bilirubin, AST/ALT, and alkaline phosphatase. Check hepatic function tests periodically.

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

**Hepatic impairment:** Tassigna 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 Tassigna. Avoid food 2 hours before and 1 hour after a dose.

Since the capsules contain lactose, Tassigna 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 Tassigna.

## 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 Information<sup>8</sup>

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\*. [0]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 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.

---

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

---

(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:

<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> PhRMA (Pharmaceutical Research and Manufacturers of America) ; *2005 Survey: Medicines in Development for Cancer: 59*

<sup>3</sup> American Cancer Society. *Cancer Facts and Figures, 2007*. Atlanta: American Cancer Society; 2007.

<sup>4</sup> American Cancer Society. *Overview: Leukemia – Chronic Myeloid (CML)*.

<sup>5</sup> [http://www.cancer.org/docroot/CRI/content/CRI\\_2\\_2\\_1x\\_How\\_Many\\_People\\_Get\\_Chronic\\_Myeloid\\_Leukemia.asp?nav=criH](http://www.cancer.org/docroot/CRI/content/CRI_2_2_1x_How_Many_People_Get_Chronic_Myeloid_Leukemia.asp?nav=criH). Last accessed Jan 22, 2007.

<sup>6</sup> Data on file. Novartis Oncology. CML Alliance Resource Pack.

<sup>7</sup> American Cancer Society.; *Cancer Facts & Figures 2006*. Atlanta: American Cancer Society; 2006

<sup>8</sup> American Cancer Society.; *Cancer Facts & Figures 2001*. Atlanta: American Cancer Society; 2001

<sup>8</sup> 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.