Understanding the Difference: Tasigna and Glivec in CML

About Chronic Myeloid Leukemia

Chronic myeloid leukemia (CML) is a cancer of the blood and bone marrow in which the body produces too many white blood cells. Chronic means a relatively slower-growing cancer that may take years to progress. Myeloid refers to the type of white blood cell being overproduced. CML is characterized in three phases: chronic phase (CP), accelerated phase (AP) and terminal blast phase (BP). Most patients find out that they have CML in the early, chronic phase and many will remain in chronic phase for a number of years without progressing to a more advanced phase of the disease.

Almost all patients with CML have a chromosomal abnormality known as the Philadelphia chromosome. The Philadelphia chromosome produces a protein called BCR-ABL that signals the bone marrow to keep making abnormal white blood cells.

CML treatments have been developed to inhibit or block the BCR-ABL protein, which helps to slow the reproduction of abnormal white blood cells.

<table>
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<th>Indications in CML</th>
<th>Tasigna® (nilotinib)</th>
<th>Glivec® (imatinib)*</th>
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<td><strong>Tasigna®</strong> (nilotinib) is approved in more than 110 countries for the treatment of adult Philadelphia chromosome-positive chronic myeloid leukemia (Ph+ CML) patients in the chronic or accelerated phases (AP). Tasigna was designed as an important treatment option for Ph+ CML patients who are resistant or intolerant to prior treatment, including Glivec® (imatinib)*.</td>
<td>Tasigna has also been approved in more than 85 global markets including the European Union (EU), Japan, Switzerland and the United States (US) for the treatment of adult patients with newly diagnosed Ph+ CML in chronic phase. With these approvals, Tasigna becomes a therapeutic option for newly diagnosed patients.</td>
<td>Glivec® (imatinib)* is indicated for newly diagnosed adult patients with Ph+ CML in the chronic phase. Glivec is also indicated for the treatment of patients with Ph+ CML in blast crisis (BC), AP, or in chronic phase after failure of interferon-alpha therapy.</td>
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**Mechanism of Action**

Tasigna is a potent and selective inhibitor of BCR-ABL and also acts to block the signal that causes the build-up of the cells.

Tasigna has an improved topological fit for the BCR-ABL kinase domain compared to Glivec, making it better able to bind to mutant forms of BCR-ABL. Tasigna is also an inhibitor of the following kinases: PDGFR, cKit, CSF-1R and DDR1a.

Glivec is a protein-tyrosine kinase inhibitor that inhibits the BCR-ABL tyrosine kinase in CML.

Glivec is also an inhibitor of the receptor tyrosine kinases for platelet-derived growth factor (PDGF) and stem cell factor (SCF), cKit, and inhibits PDGF- and SCF mediated cellular events.

*Known as Glivec® (imatinib mesylate) tablets in the US, Canada and Israel.
Data Comparing Tasigna versus Gleevec in First-Line Treatment of Ph+ CML

All filings for an indication for Tasigna to treat newly diagnosed Ph+ CML adult patients in chronic phase are based on data from the ENESTnd trial (Evaluating Nilotinib Efficacy and Safety in Clinical Trials of Newly Diagnosed Ph+ CML Patients).

ENESTnd is a Phase III randomized, open-label, multicenter trial comparing the efficacy and safety of Tasigna versus Gleevec in adult patients with newly diagnosed Ph+ CML in chronic phase. It is the longest-term comparative study of a second-generation tyrosine kinase inhibitor to date in newly diagnosed Ph+ CML patients in chronic phase.

### Trial Design

- **Randomized 1:1:1**
- **846 adult patients**
- **>210 centers**
- **35 countries**

### Primary endpoint: Major Molecular Response (MMR)

- A Polymerase Chain Reaction (PCR) test is a simple and convenient blood test used to detect BCR-ABL, the definitive cause of Ph+ CML, and can be done on the peripheral blood, with no bone marrow required.

### About Tasigna (nilotinib)

Tasigna® (nilotinib) is approved in more than 110 countries for the treatment of chronic phase and accelerated phase Philadelphia chromosome-positive chronic myelogenous leukemia (Ph+ CML) in adult patients resistant or intolerant to at least one prior therapy, including Gleevec® (imatinib), and in more than 85 countries for the treatment of adult patients with newly diagnosed Ph+ CML in chronic phase.

### Tasigna Important Safety Information

Use with caution in patients with uncontrolled or significant cardiac disease and in patients who have or may develop prolongation of QTc. Low levels of potassium or magnesium must be corrected prior to Tasigna administration. Monitor closely for an effect on the QTc interval. Baseline ECG is recommended prior to initiating therapy and as clinically indicated. Uncommon cases (0.1 to 1%) of sudden death have been reported in clinical studies in patients with significant risk factors. Cases of tumor lysis syndrome have been reported.

Use with caution in patients with liver impairment, with a history of pancreatitis and with total gastrectomy. Patients with rare hereditary problems of galactose intolerance, severe lactase deficiency or glucose-galactose malabsorption should not use Tasigna. Tasigna may cause fetal harm in pregnant women. Women taking Tasigna should not breastfeed.

The most frequent Grade 3 or 4 adverse events are hematological (neutropenia and thrombocytopenia) which are generally reversible and usually managed by withholding Tasigna temporarily or dose reduction. Monitor blood counts regularly. Pancreatitis has been reported. The most frequent non-hematologic adverse events were rash, pruritus, nausea, fatigue, headache, alopecia, myalgia, constipation and diarrhea. Most of these adverse events were mild to moderate in severity.

Please see full Prescribing Information available at www.tasigna.com.

### About Gleevec (imatinib)

Gleevec® (imatinib) is approved in more than 110 countries for the treatment of all phases of Ph+ CML, for the treatment of adult patients with KIT (CD117)-positive gastrointestinal stromal tumors (GIST), which cannot be surgically removed and/or have metastasized and for the treatment of adult patients following complete surgical removal of KIT+ GIST.

### Gleevec Important Safety Information

*Known as Gleevec® (imatinib mesylate) tablets in the US, Canada and Israel.*
Glivec can cause fetal harm in pregnant women. Glivec has been associated with severe edema (swelling) and serious fluid retention. Cytopenias (anemia, neutropenia, thrombocytopenia) are common, generally reversible and usually managed by withholding Glivec or dose reduction. Monitor blood counts regularly. Severe congestive heart failure and left ventricle dysfunction, severe liver problems including cases of fatal liver failure and severe liver injury requiring liver transplants have been reported. Caution in patients with cardiac dysfunction and hepatic dysfunction. Monitor carefully.

Bleeding may occur. Severe gastrointestinal (GI) bleeding has been reported in patients with KIT+ GIST. Skin reactions, hypothyroidism in patients taking levothyroxine replacement, GI perforation, in some cases fatal, tumor lysis syndrome which can be life threatening have also been reported with Glivec. Correct dehydration and high uric acid levels prior to treatment. Long-term use may result in potential liver, kidney, and/or heart toxicities; immune system suppression may also result from long-term use. In patients with hypereosinophilic syndrome and heart involvement, cases of heart disease have been associated with the initiation of Glivec therapy. Growth retardation has been reported in children taking Glivec. The long-term effects of extended treatment with Glivec on growth in children are unknown.

The most common side effects include fluid retention, muscle cramps or pain and bone pain, abdominal pain, loss of appetite, vomiting, diarrhea, decreased hemoglobin, abnormal bleeding, nausea, fatigue and rash. Glivec should be taken with food and a large glass of water.

Please see full Prescribing Information available at www.glivec.com.

References

*Known as Gleevec® (imatinib mesylate) tablets in the US, Canada and Israel.