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Novartis drug Tasigna® (nilotinib) secures EU approval for first and second-line treatment of Ph+ CML-CP in children

- **Tasigna is the first and only second-generation tyrosine kinase inhibitor approved in the EU for the treatment of Ph+ CML-CP in children**

- **Approval builds on a series of Tasigna regulatory milestones, including addition of Treatment-free Remission (TFR) data to EU label for adults with Ph+ CML-CP**

- **Demonstrates Novartis’ continuing commitment to CML patients**

**Basel, November 20, 2017** – Novartis announced today that the European Commission (EC) approved Tasigna® (nilotinib) for the treatment of pediatric patients with newly diagnosed Philadelphia chromosome-positive chronic myeloid leukemia in the chronic phase (Ph+ CML-CP) and pediatric patients with Ph+ CML-CP with resistance or intolerance to prior therapy including imatinib. Tasigna is the only second-generation tyrosine kinase inhibitor (TKI) currently approved in the European Union (EU) for the treatment of Ph+ CML-CP in children.

The approval follows a positive opinion issued by the European Medicines Agency’s (EMA) Committee for Medicinal Products for Human Use (CHMP) on September 14, 2017 and applies to all EU member states.

“Treatment options for children with CML have historically been limited, and with this new indication an unmet need has been addressed,” said Bruno Strigini, CEO, Novartis Oncology. “Data from two prospective studies demonstrated Tasigna is safe and effective in patients as young as two years old, which is consistent with the established safety profile of Tasigna in adults.”

This expanded indication is based on two prospective studies of nilotinib in children with Ph+ CML-CP, which were part of a formal “pediatric investigation plan” agreed upon with the EMA. A total of 69 pediatric patients received nilotinib. These pediatric patients were aged 2 to 18 years and diagnosed with either newly diagnosed Ph+ CML-CP or Ph+ CML-CP with resistance or intolerance to prior therapy including imatinib. In the newly diagnosed CML patients, the major molecular response (MMR; BCR ABL/ABL ≤0.1% International Scale [IS]) rate was 60.0% (95% confidence interval [CI]: 38.7, 78.9) at 12 cycles, with 15 patients achieving MMR. In patients with resistance or intolerance to prior therapy including imatinib, the MMR rate was 40.9% (95% CI: 26.3, 56.8) at 12 cycles, with 18 patients being in MMR. In newly diagnosed CML patients, the cumulative MMR rate was 64.0% by cycle 12. In patients with resistance or intolerance to prior therapy including imatinib, the cumulative MMR rate was 47.7% by cycle 12.

In pediatric patients, adverse reactions observed were generally consistent with those observed in adults, with the exception of hyperbilirubinemia (Grade 3/4: 13.0%), a condition where there is too much bilirubin in the blood, and transaminase elevation (AST Grade 3/4: 1.4%, ALT Grade 3/4: 8.7%) which were reported at a higher frequency than in adult patients. No deaths were reported on treatment or after treatment discontinuation in both studies.
This is the latest in a series of regulatory milestones for Tasigna. In June, Novartis achieved an important milestone for the Ph+ CML community when Tasigna became the first and only TKI to include information on stopping therapy in adult patients with Ph+ CML-CP in both the first-line setting and after switching from imatinib in the EU label and several other labels throughout the world. Novartis continues to follow the science to advance and reimagine the future of CML.

**About Ph+ CML**
CML is a type of cancer in which the body produces cancerous white blood cells. Almost all patients with CML have an abnormality known as the Philadelphia chromosome, which produces a protein called BCR-ABL. BCR-ABL causes malignant white blood cells to proliferate. Worldwide, CML is responsible for approximately 10% to 15% of all adult cases of leukemia, with an incidence of one to two cases per 100,000 people per year.

**Novartis Commitment to CML**
Novartis ongoing research in Ph+ CML has helped transform the disease from a fatal leukemia to a chronic condition in most patients. The company maintains an unwavering commitment to scientific innovation and access to care for patients worldwide. As an organization committed to patients, Novartis continues to reimagine CML by pursuing ambitious goals with courage, passion and commitment to the global CML community.

**About Tasigna (nilotinib)**
Tasigna (nilotinib) is approved in more than 122 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 Glivec® (imatinib)*, and in more than 110 countries for the treatment of adult patients with newly diagnosed Ph+ CML in chronic phase. Tasigna is approved in the European Union (EU) for the treatment of Ph+ CML in the chronic phase in pediatric patients with resistance or intolerance to prior therapy including Glivec and for the treatment of pediatric patients with newly diagnosed Ph+ CML in the chronic phase.

**IMPORTANT SAFETY INFORMATION for TASIGNA® (nilotinib) Capsules**
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. Cases of sudden death have been reported in clinical studies in patients with significant risk factors. Avoid use of concomitant drugs known to prolong the QT interval and strong CYP3A4 inhibitors. Avoid food 2 hours before and 1 hour after taking dose. Reactivation of hepatitis B can occur in patients who are chronic carriers of this virus after receiving TKI treatment.

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. If pregnancy is planned during the treatment-free remission phase, the patient must be informed of a potential need to re-initiate treatment with Tasigna during pregnancy. Women taking Tasigna should not breastfeed.

Cases of cardiovascular events included ischemic heart disease-related events, peripheral arterial occlusive disease, and ischemic cerebrovascular events have been reported. Serious cases of hemorrhage from various sites including gastrointestinal were reported in patients receiving Tasigna. Grade 3 or 4 fluid retention including pleural effusion, pericardial effusion, ascites and pulmonary edema have been reported. Cases of tumor lysis syndrome have been reported in Tasigna-treated patients who were resistant or intolerant to prior CML therapy.

In pediatric patients the long-term effects of prolonged treatment with Tasigna is unknown.
Eligible patients who are confirmed to express the typical BCR-ABL transcripts, e13a2/b2a2 or e14a2/b3a2, can be considered for treatment discontinuation. Frequent monitoring of BCR-ABL transcript levels in patients eligible for treatment discontinuation must be performed with a quantitative diagnostic test validated to measure molecular response levels with a sensitivity of at least MR4.5 (BCR-ABL/ABL ≤0.0032% IS). BCR-ABL transcript levels must be assessed prior to and during treatment discontinuation. Loss of major molecular response (MMR=BCR-ABL/ABL ≤0.1%IS) or confirmed loss of MR4 (two consecutive measures separated by at least 4 weeks showing loss of MR4 (MR4=BCR-ABL/ABL ≤0.01%IS)) will trigger treatment re-initiation within 4 weeks of when loss of remission is known to have occurred. It is crucial to perform frequent monitoring of BCR-ABL transcript levels and complete blood count with differential in order to detect possible loss of remission. For patients who fail to achieve MMR after three months of treatment re-initiation, BCR-ABL kinase domain mutation testing should be performed.

The most frequent Grade 3 or 4 adverse events are hematological (neutropenia, thrombocytopenia, anemia) which are generally reversible and usually managed by withholding Tasigna temporarily or dose reduction. Chemistry panels, including electrolytes, lipid profile, liver enzymes, and glucose should be checked prior to therapy and periodically. Tasigna can cause increases in serum lipase. The most frequent non-hematologic adverse events were rash, pruritus, nausea, fatigue, headache, alopecia, myalgia, constipation and diarrhea.

Musculoskeletal pain, myalgia, pain in extremity, arthralgia, bone pain and spinal pain may occur upon discontinuing treatment with Tasigna within the framework of attempting treatment-free remission.

Please see full Prescribing Information including Boxed WARNING at www.tasigna.com.

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

Not all indications are available in every country.

Glivec Important Safety Information
Glivec is contraindicated in patients who are hypersensitive to imatinib or any of the excipients.

Glivec can cause fetal harm when administered to a pregnant woman. Women should not become pregnant, and should be advised of the potential risk to the unborn child.

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. Reactivation of hepatitis B can occur in patients who are chronic carriers of this virus after receiving TKI treatment.

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.

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

**Disclaimer**

This press release contains forward-looking statements within the meaning of the United States Private Securities Litigation Reform Act of 1995. Forward-looking statements can generally be identified by words such as “potential,” “can,” “will,” “plan,” “expect,” “anticipate,” “look forward,” “believe,” “committed,” “investigational,” “pipeline,” “launch,” or similar terms, or by express or implied discussions regarding potential marketing approvals, new indications or labeling for the investigational or approved products described in this press release, or regarding potential future revenues from such products. You should not place undue reliance on these statements. Such forward-looking statements are based on our current beliefs and expectations regarding future events, and are subject to significant known and unknown risks and uncertainties. Should one or more of these risks or uncertainties materialize, or should underlying assumptions prove incorrect, actual results may vary materially from those set forth in the forward-looking statements. There can be no guarantee that the investigational or approved products described in this press release will be submitted or approved for sale or for any additional indications or labeling in any market, or at any particular time. Nor can there be any guarantee that such products will be commercially successful in the future. In particular, our expectations regarding such products could be affected by, among other things, the uncertainties inherent in research and development, including clinical trial results and additional analysis of existing clinical data; regulatory actions or delays or government regulation generally; our ability to obtain or maintain proprietary intellectual property protection; the particular prescribing preferences of physicians and patients; global trends toward health care cost containment, including government, payor and general public pricing and reimbursement pressures; general economic and industry conditions, including the effects of the persistently weak economic and financial environment in many countries; safety, quality or manufacturing issues, and other risks and factors referred to in Novartis AG’s current Form 20-F on file with the US Securities and Exchange Commission. Novartis is providing the information in this press release as of this date and does not undertake any obligation to update any forward-looking statements contained in this press release as a result of new information, future events or otherwise.

**About Novartis**

Novartis provides innovative healthcare solutions that address the evolving needs of patients and societies. Headquartered in Basel, Switzerland, Novartis offers a diversified portfolio to best meet these needs: innovative medicines, cost-saving generic and biosimilar pharmaceuticals and eye care. Novartis has leading positions globally in each of these areas. In 2016, the Group achieved net sales of USD 48.5 billion, while R&D throughout the Group amounted to approximately USD 9.0 billion. Novartis Group companies employ approximately 121,000 full-time-equivalent associates. Novartis products are sold in approximately 155 countries around the world. For more information, please visit http://www.novartis.com.
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