Novartis drug Tasigna® is approved by FDA as first and only CML therapy with Treatment-free Remission data in its label

- Inclusion of Treatment-free Remission (TFR) data provides additional and novel option in management of Ph+ CML-CP
- Deep and sustained molecular response included as key eligibility criteria for attempting TFR after treatment with Tasigna
- Approval granted under priority review and is based on Novartis trials evaluating TFR with Tasigna in both the first-line and second-line settings

Basel, December 22, 2017 – Novartis announced today that the US Food and Drug Administration (FDA) approved the inclusion of Treatment-free Remission (TFR) data in the Tasigna® (nilotinib) US product label. Tasigna is now the first and only BCR-ABL tyrosine kinase inhibitor (TKI) to include data about attempting treatment discontinuation in eligible adult patients with Philadelphia chromosome-positive chronic myeloid leukemia in the chronic phase (Ph+ CML-CP) after achieving sustained deep molecular response of MR4.5 (BCR-ABL1 International Scale [IS] <= 0.0032%) in its FDA-approved prescribing information. TFR is the ability to maintain a sustained molecular response* after stopping TKI therapy in patients with Ph+ CML-CP. TFR requires scheduled monitoring of BCR-ABL1 levels to identify possible loss of molecular response.

“It has long been our ambition at Novartis to make it possible for some people with CML to discontinue therapy,” said Bruno Strigini, CEO, Novartis Oncology. “We are proud that Tasigna is now the first and only TKI with TFR data in its labeling in the US and several countries around the globe. This achievement would not have been possible without the partnership of patients around the world who participated in our groundbreaking TFR trials, helping Novartis to once again reimagine what is possible for people living with CML.”

With this label update, Tasigna is the only TKI that provides defined, approved criteria to attempt and monitor TFR. This approval follows a priority review for a supplemental New Drug Application (sNDA) for Tasigna seeking the addition of TFR information and is based on safety and efficacy results from the 96-week analyses of two open label trials, ENESTfreedom and ENESTop. These trials evaluated the potential to maintain MMR (BCR-ABL1 <= 0.1%) after stopping Tasigna therapy among eligible adult patients with Ph+ CML-CP. Patients in the trials had achieved a sustained MR4.5 with Tasigna in both the first-line setting or after switching from Glivec® (imatinib)**1. The trials demonstrated that almost half of the Ph+ CML-CP patients who discontinued Tasigna remained in TFR approximately two years after stopping treatment1. Among patients who did lose molecular response during the TFR phase of the trials, nearly all regained MMR when Tasigna therapy was promptly reinitiated1. The safety data are consistent with previously published studies and the known safety profile of Tasigna1.

The TFR data in the Tasigna label approved by the FDA included the use of the MolecularMD MRDx™ BCR-ABL test, a FDA-authorized companion diagnostic validated to measure BCR-ABL transcript levels down to MR4.51. Discontinuation of Tasigna should only be attempted under the close supervision of a physician. Frequently scheduled patient monitoring after
Tasigna discontinuation is required so that possible loss of MMR and MR4.0 (BCR-ABL1 IS <= 0.01%) is quickly identified and treatment re-initiation is started promptly1.

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 accounts 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.

About ENESTfreedom
ENESTfreedom (Evaluating Nilotinib Efficacy and Safety in Clinical Trials – Following REsponsE in De nOvo CML-CP Patients) is an open label Phase II study of 215 Ph+ CML-CP patients, conducted at 132 sites across 19 countries. The trial evaluated stopping treatment in 190 adults with Ph+ CML-CP in patients who had achieved a response of MR4.5 with Tasigna as a first-line treatment, who sustained deep molecular response for one year prior to treatment discontinuation.

Results from the ENESTfreedom study found that 48.9% of 190 CML patients (confidence interval [CI] 95%: 41.6%-56.3%) were able to discontinue therapy and remain in MMR at 96 weeks1. Of the 88 patients who promptly restarted treatment with Tasigna due to loss of MMR by the cut-off date, 98.9% were able to regain MMR (n=87)1. One patient discontinued the study at 7.1 weeks without regaining MMR after reinitiating treatment with Tasigna1. Patients who discontinued therapy were continually monitored for possible loss of molecular response after treatment discontinuation. BCR-ABL transcript levels and complete blood count with differential were monitored monthly for one year, then every 6 weeks for the second year, and every 12 weeks thereafter1.

The safety data observed in this trial are consistent with the known safety profile of Tasigna. AEs (all grades) in the predefined musculoskeletal pain grouping decreased from 34.0% to 9.0% during the first and second 48 weeks of the TFR phase, respectively, versus 17.0% during the treatment consolidation phase1.

About ENESTop
ENESTop (Evaluating Nilotinib Efficacy and Safety Trial) is an open label Phase II study of 163 Ph+ CML-CP patients, conducted at 63 sites across 18 countries. The trial evaluated stopping treatment in 126 adults with Ph+ CML-CP in patients who had been previously treated with Glivec, and then switched to Tasigna, who achieved and sustained molecular response for one year prior to treatment discontinuation.

ENESTop showed that more than half (53.2%) of patients were able to remain in TFR at 96 weeks (95% CI: 44.1%-62.1%)1. In the study, 56 patients with confirmed loss of MR4.0 or loss of MMR restarted Tasigna by the cut-off date1. Of these patients, 92.9% (n=52) regained both MR4.0 and MR4.51. Patients who discontinued therapy were continually monitored for possible loss of molecular response after treatment discontinuation. BCR-ABL transcript levels and complete blood count with differential were monitored monthly for one year, then every 6 weeks for the second year, and every 12 weeks thereafter1.

The safety data observed in this trial are consistent with the known safety profile of Tasigna. Rates of musculoskeletal pain-related AEs (all grades) decreased from 47.9% to 15.1% during the first and second 48 weeks of the TFR phase, respectively, versus 13.7% during the treatment consolidation phase1.

Novartis Commitment to CML
Evaluating more than 1,000 patients, the Tasigna TFR clinical trial program is among the most extensive in the industry. This large international program designed to assess TKI discontinuation includes ENESTfreedom and ENESTop, as well as two other ongoing company-sponsored TFR studies and multiple investigator-initiated studies. Novartis’
commitment to innovation builds upon existing evidence to explore the next advance for the care of people with 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 for the global CML community.

About Tasigna
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 fatal 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.


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.
Novartis is on Twitter. Sign up to follow @Novartis at http://twitter.com/novartis and @NovartisCancer at https://twitter.com/novartiscancer
For Novartis multimedia content, please visit www.novartis.com/news/media-library
For questions about the site or required registration, please contact media.relations@novartis.com

*No loss of MMR (BCR-ABL1 <= 0.1%) in newly diagnosed patients, and no loss of MMR or no confirmed loss of MR4.0 (BCR-ABL1 <= 0.01%) in patients resistant or intolerant to prior treatment including imatinib.

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

References
1. Tasigna (nilotinib) Prescribing Information. East Hanover, New Jersey, USA: Novartis Pharmaceuticals Corporation; December 2017.

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