Novartis receives EU approval for Jakavi® in polycythemia vera, first targeted therapy approved for patients with this rare blood cancer

- Jakavi® (ruxolitinib) approved by the European Commission for adult patients with polycythemia vera (PV) resistant to or intolerant of hydroxyurea
- PV is a rare blood cancer associated with an overproduction of blood cells that can lead to serious cardiovascular complications if left untreated
- Jakavi is the only JAK 1/2 inhibitor available to treat PV and is also currently approved in more than 80 countries to treat myelofibrosis

Basel, March 17, 2015 – Novartis announced today that the European Commission has approved Jakavi® (ruxolitinib) for the treatment of adult patients with polycythemia vera (PV) who are resistant to or intolerant of hydroxyurea. Jakavi is the first targeted treatment approved by the European Commission for these patients.

PV is a rare and incurable blood cancer associated with an overproduction of blood cells that can cause serious cardiovascular complications, such as blood clots, stroke, and heart attack. Approximately 25% of patients with PV develop resistance to or intolerance of hydroxyurea and are considered to have uncontrolled disease. This is typically defined as hematocrit levels greater than 45%, elevated white blood cell count and/or platelet count, and may be accompanied by debilitating symptoms and/or an enlarged spleen.

“The European Commission’s approval of Jakavi is encouraging news for patients,” said Dr. Claire Harrison, study investigator and Consultant Hematologist, Guy’s and St. Thomas’ NHS Foundation Trust, London. “Jakavi will fill an unmet need as the first treatment shown to significantly improve hematocrit, as well as symptom control and reduce spleen size in patients with polycythemia vera resistant to or intolerant of hydroxyurea.”

The approval is based on data from the pivotal Phase III RESPONSE clinical trial demonstrating that a significantly greater proportion of patients achieved the composite primary endpoint of hematocrit control without use of phlebotomy and spleen size reduction, key measures of disease control, when treated with Jakavi compared to best available therapy (21% compared to 1%, respectively; p<0.0001). In the study, a 50% or more improvement in PV-related symptoms was seen in 49% of Jakavi-treated patients compared to 5% of patients treated with best available therapy.

“The approval of Jakavi in polycythemia vera underscores what’s possible in today’s era of precision oncology research,” said Bruno Strigini, President, Novartis Oncology. “Jakavi specifically targets the JAK-STAT pathway, which regulates blood cell production and is known to play a key role in the underlying mechanism of this disease, bringing patients and physicians a new way to treat polycythemia vera.”
Overall, non-hematologic adverse events (AEs) were consistent with those previously seen in other Jakavi studies in PV and myelofibrosis\(^2,6,7\). Within the first 32 weeks of treatment, the most common Grade 3 or 4 hematologic AEs in the Jakavi-treatment arm were anemia (1.8%) and thrombocytopenia (5.5%)\(^2\). The most common non-hematologic AEs were dizziness (15.5%), constipation (8.2%) and herpes zoster (6.4%)\(^2\). The three most frequent non-hematological laboratory abnormalities (any Grade) were hypercholesterolemia (30.0%), raised alanine aminotransferase (22.7%) and raised aspartate aminotransferase (20.9%), which were mainly Grade 1 and 2\(^2\).

The European Commission approval applies to all 28 EU member states, plus Iceland, Norway and Liechtenstein. Additional regulatory applications for ruxolitinib in PV are currently ongoing in countries worldwide, and further regulatory filings are under review by health authorities. Ruxolitinib, which is marketed in the US by Incyte Corporation as Jakavi\(^®\), received approval in December 2014 from the US Food and Drug Administration (FDA) for the treatment of patients with PV who have had an inadequate response to or are intolerant of hydroxyurea.

About the Pivotal Clinical Trial
RESPONSE is a global, randomized, open-label trial conducted at more than 90 trial sites. 222 patients with PV resistant to or intolerant of hydroxyurea were randomized 1:1 to receive either Jakavi (starting dose of 10 mg twice daily) or best available therapy, which was defined as investigator-selected monotherapy or observation only. The Jakavi dose was adjusted as needed throughout the trial. In the Jakavi arm, patients had a PV diagnosis for a median of 8.2 years and had previously received hydroxyurea for a median of approximately three years. Most patients (>80%) had received at least two phlebotomies in the last 24 weeks prior to screening\(^2\). Patients were classified as intolerant or resistant to hydroxyurea based on the modified European LeukemiaNet (ELN) defined criteria\(^8\).

The primary endpoint of the trial was the proportion of patients whose hematocrit was controlled without phlebotomy eligibility from week 8 through 32 (with no more than one phlebotomy eligibility between randomization and week 8) and whose spleen volume was reduced by 35% or more from baseline as assessed by imaging at week 32. Patients in the trial who were deemed to be eligible for phlebotomy had hematocrit that was greater than 45% and had increased three or more percentage points from the time they entered the trial (e.g., at baseline), or hematocrit greater than 48%. In addition, efficacy was further assessed using two key secondary endpoints: durable primary response and complete hematological remission. Other endpoints include safety and symptom improvement (as measured by the MPN-SAF 14-item total symptom score)\(^2\).

About Polycythemia Vera
PV is a rare and incurable blood cancer associated with an overproduction of blood cells in the bone marrow that affects roughly one to three people per 100,000 globally\(^1,9\). The disease is driven by the dysregulation of the JAK-STAT pathway\(^10\). It is typically characterized by elevated hematocrit, the volume percentage of red blood cells in whole blood, which can lead to a thickening of the blood and an increased risk of blood clots, as well as an elevated white blood cell and platelet count\(^1\). This can cause serious cardiovascular complications, such as stroke and heart attack, resulting in increased morbidity and mortality\(^11\). Additionally, patients with PV may have an enlarged spleen and symptoms that are frequent and burdensome, with an overall impact on quality of life similar to that seen with myelofibrosis\(^8,12\).

A common PV treatment includes phlebotomy, a procedure to remove blood from the body to reduce the concentration of red blood cells, which is used to help maintain a hematocrit level below 45%\(^1,11\). However, phlebotomy is usually unsuitable as a permanent treatment option due to its inability to control symptoms or effectively manage the overproduction of red blood cells, therefore cytoreductive agents, such as hydroxyurea, may be added\(^11\). For patients requiring phlebotomy in combination with
hydroxyurea, hematocrit may fluctuate and remain at unsafe levels for significant periods of time. Unfortunately, approximately 25% of PV patients become resistant to or intolerant of hydroxyurea treatment according to ELN criteria, resulting in inadequate disease control and an increased risk of progression.

**About Jakavi**

Jakavi (ruxolitinib) is an oral inhibitor of the JAK 1 and JAK 2 tyrosine kinases. Jakavi is approved by the European Commission for the treatment of adult patients with polycythemia vera (PV) who are resistant to or intolerant of hydroxyurea and for the treatment of disease-related splenomegaly or symptoms in adult patients with primary myelofibrosis (also known as chronic idiopathic myelofibrosis), post-polycythemia vera myelofibrosis or post-essential thrombocythemia myelofibrosis. Jakavi is approved in more than 80 countries for patients with myelofibrosis, including countries in the European Union, Canada, Japan and some countries in Asia, Latin and South America. Additional worldwide regulatory filings are underway in myelofibrosis and PV.

Novartis licensed ruxolitinib from Incyte Corporation for development and commercialization outside the United States. Jakavi is marketed in the United States by Incyte Corporation as Jakafi® for the treatment of patients with PV who have had an inadequate response to or are intolerant of hydroxyurea and for the treatment of patients with intermediate or high-risk myelofibrosis.

The recommended starting dose of Jakavi in PV is 10 mg given orally twice daily. The recommended starting dose of Jakavi in myelofibrosis is 15 mg twice daily for patients with a platelet count between 100,000 cubic millimeters (mm³) and 200,000 mm³, and 20 mg twice daily for patients with a platelet count of >200,000 mm³. Doses may be titrated based on safety and efficacy. There is limited information to recommend a starting dose for myelofibrosis and PV patients with platelet counts between 50,000/mm³ and <100,000/mm³. The maximum recommended starting dose in these patients is 5 mg twice daily, and patients should be titrated cautiously.

Jakavi is a registered trademark of Novartis AG in countries outside the United States. Jakafi is a registered trademark of Incyte Corporation. The safety and efficacy profile of Jakavi has not yet been established outside the approved indication.

**Jakavi Important Safety Information for Treatment of Myelofibrosis (MF) and Polycythemia Vera (PV)**

Jakavi can cause serious side effects, including a decrease in blood cell count and infections. Complete blood count monitoring is recommended. Dose reduction or interruption may be required in patients with any hepatic impairment or severe renal impairment or in patients developing hematologic adverse reactions such as thrombocytopenia, anemia and neutropenia. Dose reductions are also recommended when Jakavi is co-administered with strong CYP3A4 inhibitors or fluconazole. Use of Jakavi during pregnancy is not recommended, and women should avoid becoming pregnant during Jakavi therapy. Women taking Jakavi should not breast feed. Progressive multifocal leukoencephalopathy (PML) has been reported. Physicians should be alert for neuropsychiatric symptoms suggestive of PML. Hepatitis B viral load (HBV-DNA titer) increases have been reported in patients with chronic HBV infections. Patients with chronic HBV infection should be treated and monitored according to clinical guidelines. Non-melanoma skin cancer (NMSC) has been reported in Jakavi treated patients. Periodic skin examination is recommended. Very common adverse reactions in MF (>10%) include urinary tract infections, anemia, thrombocytopenia, neutropenia, hypercholesterolemia, dizziness, headache, alanine aminotransferase increased, aspartate aminotransferase increased, bruising and weight gain. Common adverse reactions in MF (1 to 10%) include herpes zoster and flatulence. Uncommon adverse reactions in MF include tuberculosis. Very common adverse reactions in PV (>10%) include anemia, thrombocytopenia, hypercholesterolemia, hypertriglyceridemia,
dizziness, alanine aminotransferase increased and aspartate aminotransferase increased. Common adverse reactions in PV (1 to 10%) include urinary tract infections, herpes zoster, weight gain, constipation and hypertension.

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

Disclaimer
The foregoing release contains forward-looking statements that can be identified by words such as “encouraging,” “will,” “ongoing,” “under review,” “underway,” or similar terms, or by express or implied discussions regarding potential new indications or labeling for Jakavi, or regarding potential future revenues from Jakavi. You should not place undue reliance on these statements. Such forward-looking statements are based on the current beliefs and expectations of management regarding future events, and are subject to significant known and unknown risks and uncertainties. Should one or more of these risks or uncertainties materialize, actual results may vary materially from those set forth in the forward-looking statements. There can be no guarantee that Jakavi will be submitted or approved for any additional indications or labeling in any market, or at any particular time. Nor can there be any guarantee that Jakavi will be commercially successful in the future. In particular, management’s expectations regarding Jakavi could be affected by, among other things, unexpected regulatory actions or delays or government regulation generally; the uncertainties inherent in research and development, including unexpected clinical trial results and additional analysis of existing clinical data; the company’s ability to obtain or maintain proprietary intellectual property protection; general economic and industry conditions; global trends toward health care cost containment, including ongoing pricing pressures; unexpected 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, eye care and cost-saving generic pharmaceuticals. Novartis is the only global company with leading positions in these areas. In 2014, the Group achieved net sales of USD 58 billion, while R&D throughout the Group amounted to approximately USD 9.9 billion (USD 9.6 billion excluding impairment and amortization charges). As of December 31, 2014 Novartis Group companies employed approximately 133,000 full-time-equivalent associates. Novartis products are available in more than 180 countries around the world. For more information, please visit http://www.novartis.com.

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