Novartis drug Rydapt® (midostaurin) receives EU approval for newly diagnosed FLT3-mutated acute myeloid leukemia (AML) and three types of advanced systemic mastocytosis (SM)

- Significant overall survival benefit seen with Rydapt, the first targeted treatment for newly diagnosed FLT3-mutated AML approved in the EU
- As the first and only therapy for advanced SM in the EU, Rydapt offers a new treatment option for patients with this group of rare and life-threatening diseases
- Approval based on data from largest landmark trials in AML and advanced SM to date; first major development in targeted AML treatment in more than 25 years

Basel, September 20, 2017 – Novartis today announced that the European Commission (EC) approved Rydapt® (midostaurin) for two indications in rare, hard-to-treat cancers. Rydapt is approved for use in combination with standard daunorubicin and cytarabine induction and high-dose cytarabine consolidation chemotherapy, and for patients in complete response followed by Rydapt single agent maintenance therapy, for adults with newly diagnosed acute myeloid leukemia (AML) who are FLT3 mutation-positive. It was also cleared for use as monotherapy for the treatment of adults with aggressive systemic mastocytosis (ASM), systemic mastocytosis with associated hematological neoplasm (SM-AHN) or mast cell leukemia.

The approval follows a positive opinion issued by the European Medicines Agency's (EMA) Committee for Medicinal Products for Human Use (CHMP) on July 20, 2017 and applies to all 28 EU member states, plus Iceland, Liechtenstein and Norway. Rydapt represents the first and only targeted therapy for FMS-like tyrosine kinase 3 (FLT3)-mutated AML and the only treatment for three subtypes of SM, collectively known as advanced SM, in the EU, all of which have limited life expectancy and few treatment options. Rydapt represents the first major advancement for the treatment of patients with newly diagnosed FLT3-mutated AML in more than 25 years.

“Novartis is proud that we can deliver Rydapt, a breakthrough medicine, to patients with serious and hard-to-treat diseases where there are few treatment options,” said Bruno Strigini, CEO, Novartis Oncology. “For patients with FLT3-mutated AML, there have been no meaningful advancements in more than 25 years and with Rydapt they now have a targeted medicine that could significantly extend their lives.”

For newly diagnosed FLT3-mutated AML, the approval is based on data from the RATIFY (CALGB 10603 [Alliance]) trial, which was conducted in collaboration with the Alliance for Clinical Trials in Oncology and 13 international cooperative groups. RATIFY is the largest trial to date among people with this specific type of AML and results of the trial were recently published in the New England Journal of Medicine (NEJM). The study showed a 23% reduction in the risk of death with Rydapt plus standard chemotherapy compared with placebo plus standard chemotherapy. Median overall survival of 74.7 months and 25.6 months,
respectively (hazard ratio [HR] = 0.77, 95% confidence interval [CI], 0.63, 0.95; one-sided p=0.0078)

In the RATIFY trial, the most frequent adverse reactions (incidence greater than or equal to 30%) in the Rydapt plus standard chemotherapy arm were febrile neutropenia, nausea, exfoliative dermatitis, vomiting, headache, petechiae (small red skin spots) and pyrexia. The most frequent Grade 3/4 adverse reaction (greater than or equal to 5%) was febrile neutropenia, lymphopenia, device-related infection, exfoliative dermatitis, hyperglycemia and nausea.

For advanced SM, the approval is based on two single-arm open-label multicenter trials, including the Phase II study (CPKC412D2201), the largest prospective trial ever conducted in this rare disorder, the results of which were also published in NEJM. The efficacy of Rydapt was established using modified Valent criteria, with patients demonstrating an overall response rate, defined as a major or partial response, of 59.6% (95% CI, 48.6, 69.8%). Efficacy was also assessed in a post-hoc analysis using the 2013 International Working Group-Myeloproliferative Neoplasms Research and Treatment-European Competence Network on Mastocytosis (IWG-MRT-ECNM) consensus criteria (n=113). This assessment estimated an overall response rate of 28.3% (95% CI, 20.2, 37.6).

In advanced SM, the most frequent adverse reactions were nausea, vomiting, diarrhea, peripheral edema and fatigue. The most frequent Grade 3/4 adverse reactions were fatigue, sepsis, pneumonia, febrile neutropenia and diarrhea.

Rydapt Ongoing Clinical Development
In order to further investigate the potential of Rydapt in AML, Novartis is planning a Phase III study in newly diagnosed AML patients without a FLT3 mutation (wildtype).

About AML
AML is the most common acute leukemia, or blood cancer, in adults; it accounts for approximately 25% of all adult leukemias worldwide, with the highest incidence rates occurring in the US, Europe and Australia. It also has the lowest survival rate of all adult leukemias.

In AML, white blood cells are not able to mature and instead build up an accumulation of “blasts,” blocking room for normal blood cells. Mutations in specific genes, such as FLT3, are found in many cases of the disease. Genetic testing for mutations in newly diagnosed AML patients can help to determine prognosis and potential treatment strategies.

In the EU, there are more than 18,000 estimated new cases of AML diagnosed each year. Approximately one-third of AML patients have a FLT3 gene mutation. FLT3 is a type of cell-surface receptor, which plays a role in increasing the number of certain blood cells. The FLT3 gene mutation can result in faster disease progression, higher relapse rates and lower rates of survival than other forms of AML.

About Advanced SM
In advanced SM, the uncontrolled growth of neoplastic mast cells causes organ damage (e.g., liver dysfunction), low blood counts and weight loss. People with the disease also suffer from debilitating systemic symptoms such as pruritus (severe itching of the skin) caused by mast cells releasing inflammatory mediators, such as histamine, into the blood.

The uncontrolled proliferation of mast cells is caused in many people by a KIT gene mutation – the most common mutation, encoding the D816V substitution, occurs in approximately 90% of patients. The KIT gene mutation results in activation of the KIT enzyme, which triggers the abnormal proliferation and survival of mast cells.
About Rydapt® (midostaurin)

Rydapt® (midostaurin) is an oral, targeted therapy, a type of treatment that interferes with certain pathways that are involved in the growth, progression and spread of cancer. Rydapt inhibits multiple kinases, including FLT3, which help regulate many essential cell processes, interrupting cancer cells' ability to grow and multiply. Rydapt induces cell death in leukemic cells expressing FLT3 ITD or TKD mutant receptors, or in cells overexpressing FLT3 wildtype receptors.1

Rydapt also inhibits the activity of the kinase KIT (wild type and D816V mutant), inhibiting mast cell proliferation, survival and histamine release. In addition, Rydapt inhibits several other receptor tyrosine kinases such as PDGFRα/β, VEGFR2, and members of the serine/threonine kinase PKC family, inhibiting signaling of the respective growth factors in cells, resulting in growth arrest.1

During the past decade, targeted therapies have become known for extending the lives of patients across multiple tumor types.

Rydapt is also approved in the US, Switzerland and Canada. Indications vary by country and not all indications are available in every country. The safety and efficacy profile of Rydapt has not yet been established outside the approved indications. Because of the uncertainty of clinical trials, there is no guarantee that Rydapt will become commercially available for additional indications anywhere else in the world.

Rydapt Important Safety Information FROM THE RYDAPT EU SmPC

Patients who are allergic to midostaurin or any of the ingredients in Rydapt should not take Rydapt. If a patient taking Rydapt develops signs of an allergic reaction, they should seek medical help immediately. Signs of an allergic reaction include difficulty breathing or swallowing, dizziness, swelling of the face, lips, tongue or throat, severe itching of the skin, with a red rash or raised bumps.

The following medicines should be avoided during treatment with Rydapt: medicines used to treat tuberculosis, such as rifampicin; medicines used to treat epilepsy, such as carbamazepine or phenytoin; enzalutamide, a medicine used to treat prostate cancer; St. John's Wort, a herbal medicine used to treat depression. Patients should tell their doctor about all the medicines they are taking, have recently taken or might take.

Before taking Rydapt, patients should tell their doctor if they have any infections, a heart disorder or lung problems. Patients on Rydapt who experience the following symptoms should get medical help right away: fever, sore throat or mouth ulcers (signs of infections); new or worsening symptoms such as fever, cough with or without mucous, chest pain, trouble breathing or shortness of breath (signs of infections or lung problems); chest pain or discomfort, light headedness, fainting, dizziness, blue discoloration of the lips, hands or feet, shortness of breath, or swelling of the lower limbs (edema) or skin (signs of heart problems). Depending on the severity, doctors may adjust, temporarily stop or completely discontinue treatment with Rydapt.

For patients on Rydapt, regular blood tests should be performed in order to monitor the amount of blood cells (white blood cells, red blood cells and platelets) and electrolytes (e.g. calcium, potassium, magnesium). Patients' heart and lung function will be checked regularly.

Rydapt is not recommended during pregnancy because it may harm an unborn baby. Pregnancy testing should be done before treatment start to make sure the patient is not pregnant. Effective birth control should be used during treatment with Rydapt and for at least four months after stopping Rydapt. If a hormonal contraceptive is used, a barrier method, such as a condom or a diaphragm must also be used. Rydapt may harm a baby. Women
should not breastfeed during treatment with Rydapt and for at least four months after stopping the treatment. Rydapt may reduce fertility in women and men.

Rydapt contains alcohol, which may be harmful for patients with alcohol related problems, epilepsy or liver problems, or who are pregnant or breast feeding. Rydapt contains macrogolglycerol hydroxystearate, which may cause stomach discomfort and diarrhea.

Some side effects in patients with AML could be serious: weakness, spontaneous bleeding or bruising, frequent infections with signs such as fever, chills, sore throat or mouth ulcers (signs of a low level of blood cells); severe shortness of breath, labored and unusually rapid breathing, dizziness, light headedness, confusion and extreme tiredness (signs of acute respiratory distress syndrome); infections, fever, low blood pressure, decreased urination, rapid pulse, rapid breathing (signs of sepsis or neutropenic sepsis).

Some side effects in patients with ASM, SM-AHN and mast cell leukemia could be serious: weakness, spontaneous bleeding or bruising, frequent infections with signs such as fever, chills, sore throat or mouth ulcers (signs of a low level of blood cells); fever, cough, difficult or painful breathing, wheezing, chest pain when breathing (signs of pneumonia); infections, fever, dizziness, light headedness, decreased urination, rapid pulse, rapid breathing (signs of sepsis or neutropenic sepsis); vomiting of blood, black or bloody stools (signs of gastrointestinal bleeding).

Please see full prescribing information for Rydapt.

Disclaimer
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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 119,000 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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