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

- Recommendation based on largest trial in FLT3-mutated AML to date, showing 23% reduction in the risk of death with Rydapt treatment regimen

- If approved, Rydapt would represent the first targeted treatment for newly diagnosed FLT3-mutated AML in the EU

- Rydapt would be the first and only EMA-approved therapy for advanced SM, a group of rare, life-threatening conditions

**Basel, July 21, 2017** – Novartis today announced that the European Medicines Agency’s (EMA) Committee for Medicinal Products for Human Use (CHMP) adopted a positive opinion recommending approval of Rydapt® (midostaurin) for the treatment of adults with newly diagnosed acute myeloid leukemia (AML) who are FLT3 mutation-positive. If approved by the European Commission (EC), Rydapt will be indicated 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 adult patients with newly diagnosed AML who are FLT3 mutation-positive. Rydapt was also recommended for approval as monotherapy for the treatment of adult patients with aggressive systemic mastocytosis (ASM), systemic mastocytosis with associated hematological neoplasm (SM-AHN) or mast cell leukemia.

If approved, Rydapt will be the first targeted treatment available in the European Union (EU) for newly diagnosed FLT3 mutation-positive AML patients and advanced systemic mastocytosis (SM) patients. The opinion follows the recent US Food and Drug Administration (FDA) 2017 approval of Rydapt for FLT3-mutated AML and advanced SM on April 28 and the Swissmedic approval on May 4.

“Novartis is dedicated to bringing new treatment options to patients with rare diseases, including AML and advanced SM, which have seen limited treatment developments in the past 25 years,” said Bruno Strigini, CEO, Novartis Oncology. “We are pleased with the positive recommendation from the CHMP and excited to move a step closer to bringing this much-needed treatment to these patients across Europe.”

AML is a rare and aggressive cancer of the blood and bone marrow. In the EU, there are over 18,000 estimated new cases of AML each year. Approximately one-third of AML patients will have a FLT3 gene mutation.

FMS-like tyrosine kinase 3 (FLT3) is a type of cell-surface receptor which plays a role in increasing the number of certain blood cells and the FLT3 gene mutation can result in faster disease progression, higher relapse rates and lower rates of survival than other forms of AML. Prior to the approval of Rydapt in the US, the AML therapeutic strategy had remained relatively unchanged for more than 25 years.
Advanced SM is a rare blood disorder characterized by uncontrolled growth and accumulation of mast cells – mediators of allergic responses – in one or more organs\(^9\). In advanced SM, mast cells accumulate in such high quantities that they begin to cause organ damage\(^9\). Median overall survival is currently less than six months for mast cell leukemia\(^10\), two years for SM-AHN and 3.5 years for ASM\(^11\).

The EC typically adheres to the recommendation of the CHMP and delivers its final decision within approximately two to three months. The decision will be applicable to all 28 EU member states, plus Iceland, Liechtenstein and Norway.

The positive opinion is based on the Phase III RATIFY (CALGB 10603 [Alliance]) clinical trial, which was conducted in collaboration with the Alliance for Clinical Trials in Oncology and 13 international cooperative groups. In the trial, newly diagnosed FLT3 mutation-positive patients who received Rydapt plus standard chemotherapy experienced significant improvement in overall survival with a 23% reduction in the risk of death compared with placebo plus standard chemotherapy, with median overall survival of 74.7 months and 25.6 months, respectively (hazard ratio [HR] = 0.77, 95% CI, 0.63, 0.95; one-sided p=0.0078)\(^1\). The full data from the RATIFY trial were recently published in the *New England Journal of Medicine (NEJM)*\(^12\).

Event-free survival (EFS; event defined as no complete remission within 60 days of the start of induction therapy, relapse or death) was significantly longer for Rydapt plus chemotherapy versus placebo plus standard chemotherapy (median of 8.2 months compared to 3.0 months, HR = 0.78, 95% CI 0.66, 0.93 and one-sided p=0.0024). RATIFY is the largest worldwide clinical trial in newly diagnosed FLT3-mutated AML to date, as 3,277 AML patients were screened for the FLT3 mutation and 717 patients were enrolled\(^1\).

In the Phase III AML 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 non-hematologic Grade 3/4 adverse reaction was febrile neutropenia\(^1\).

The recommendation in advanced SM is based on two single-arm open-label multicenter trials, including the Phase II study (CPKC412D2201), which was the largest prospective trial ever conducted in this rare disorder. 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% confidence interval [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)\(^1\).

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\(^1\).

**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 in adults; it accounts for approximately 25% of all adult leukemias worldwide, with the highest incidence rates occurring in the US, Europe and Australia\(^13\). It also has the lowest survival rate of all adult leukemias\(^13\).
AML prevents white blood cells from maturing, causing an accumulation of “blasts,” which do not allow room for the normal blood cells. Mutations in specific genes are found in many cases of AML, and genetic testing for mutations in newly diagnosed AML patients can help to determine prognosis and potential treatment strategies.

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. Patients 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, multi-targeted inhibitor of multiple kinases, including FLT3 and KIT, which help regulate many essential cell processes, interrupting cancer cells’ ability to grow and multiply.

In the US, Rydapt is FDA-approved for the treatment of adults with newly diagnosed AML who are FMS-like tyrosine kinase 3 mutation-positive (FLT3+) as detected by an FDA-approved test, in combination with standard cytarabine and daunorubicin induction and cytarabine consolidation chemotherapy. Rydapt is not indicated in the US as a single-agent induction therapy for the treatment of patients with AML. For a description of the experience with single-agent treatment beyond induction and consolidation, healthcare professionals in the US should refer to the Clinical Studies section of the US Prescribing Information (14.1). Rydapt is also approved to treat adult patients with aggressive systemic mastocytosis (ASM), systemic mastocytosis with associated hematological neoplasm (SM-AHN) or mast cell leukemia, collectively referred to as advanced systemic mastocytosis (SM).

The full US Prescribing Information for Rydapt can be found at: https://www.pharma.us.novartis.com/sites/www.pharma.us.novartis.com/files/rydapt.pdf

Rydapt is also approved in Switzerland, for use in combination with standard induction and consolidation chemotherapy, followed by maintenance monotherapy for treatment of newly diagnosed adult AML patients who have an FLT3 mutation. Rydapt is indicated in Switzerland for the treatment of adult patients with advanced SM.

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

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 trouble breathing, flushing, chest pain, throat tightness, and swelling of lips, mouth or throat.

Rydapt should be not be used during pregnancy since Rydapt may harm an unborn baby. Pregnancy testing should be conducted for women who might become pregnant. Effective birth control should be used during treatment and for at least four months after stopping Rydapt. If a patient becomes pregnant or thinks she may be, the patient should tell their doctor right away. Women should not breastfeed during treatment with Rydapt and for at least four months after the final dose. Men taking Rydapt who have female partners that are able to...
become pregnant should use effective birth control during his treatment with Rydapt and for at least four months after the last Rydapt dose. Rydapt may cause fertility problems in women and men, which may affect their ability to have children.

Rydapt may cause lung problems that may lead to death. Patients on Rydapt who develop a new or worsening cough, shortness of breath, or chest discomfort should get medical help right away. These may be signs of serious lung problems.

Common side effects reported during Rydapt treatment for AML included low level of white blood cells with fever (febrile neutropenia); nausea; redness, pain or ulcers inside the mouth (mucositis); vomiting; headache; bruising; muscle or bone pain; nose bleeds; device-related infection; high blood sugar levels (hyperglycemia) and upper respiratory infections.

Common side effects reported during treatment for ASM, SM-AHM or mast cell leukemia included nausea; vomiting; diarrhea; swelling of the hands, feet or ankles; muscle or bone pain; stomach-area pain; tiredness; upper respiratory infection; constipation; fever; headache and trouble breathing.

If side effects including nausea, vomiting, and diarrhea occur, get worse or do not go away during treatment with Rydapt, patients should contact their doctor. Depending on the side effect and/or severity of the side effect that occur, their doctor may decrease their dose, temporarily stop, or completely stop treatment with Rydapt.

Patients should tell their doctor about all the medicines they take, including prescription and over-the-counter medicines, vitamins and herbal supplements. Rydapt may affect how these medicines work or these other medicines may affect how Rydapt works.

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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