Rydapt® (midostaurin) – New orphan drug approval

- On April 28, 2017 the FDA announced the approval of Novartis' Rydapt (midostaurin) capsules for the following: in combination with standard cytarabine and daunorubicin induction and cytarabine consolidation chemotherapy, for the treatment of adult patients with newly diagnosed acute myeloid leukemia (AML) who are FLT3 mutation-positive, as detected by a FDA approved test; and for the treatment of adult patients with aggressive systemic mastocytosis (ASM), systemic mastocytosis (SM) with associated hematological neoplasm (SM-AHN), or mast cell leukemia (MCL).
    - Rydapt is not indicated as a single-agent induction therapy for the treatment of patients with AML.
- Rydapt is approved for use with a companion diagnostic, the LeukoStrat® CDx FLT3 Mutation Assay, which is used to detect the FLT3 mutation in patients with AML.
- AML is a rapidly progressing cancer that forms in the bone marrow and results in an increased number of white blood cells in the bloodstream. The National Cancer Institute estimates that in 2017 approximately 21,380 people will be diagnosed with AML and 10,590 may die of the disease. About one-third of these AML patients will 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.
- Advanced SM, which includes ASM, SM and SM-AHN, is a rare blood disorder characterized by uncontrolled growth and accumulation of mast cells in one or more organs, which may eventually lead to organ damage. Median overall survival is currently less than 6 months for MCL, 2 years for SM-AHN, and 3.5 years for ASM.
    - The uncontrolled proliferation and survival of mast cells is caused mostly by a KIT gene mutation, which occurs in approximately 90% of patients with advanced SM.
- Rydapt is a 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.
- The efficacy of Rydapt for the treatment of AML was demonstrated in a study of 717 patients with newly diagnosed FLT3 mutation-positive AML. Patients were randomized to receive Rydapt or placebo in combination with chemotherapy. Outcome measures included overall survival (OS) and event-free survival (EFS).
    - Patients in the Rydapt plus chemotherapy group experienced a significant improvement in OS vs. placebo plus chemotherapy (hazard ratio [HR] = 0.77, 95% CI: 0.63, 0.95; p = 0.016).
    - EFS, defined as a failure to obtain a complete remission (CR) within 60 days of initiation of therapy, or relapse, or death from any cause, showed a statistically significant improvement with a median of 8.2 months for Rydapt plus chemotherapy vs. 3 months for placebo plus chemotherapy (HR = 0.78, 95% CI: 0.66, 0.93; p = 0.005).
- The efficacy of Rydapt as a single agent for the treatment of advanced SM was evaluated in a single-arm, open-label clinical study of 116 patients. This study demonstrated a 21% (95% CI: 13, 31) response rate on the basis of confirmed CR plus incomplete remission by 6 cycles of Rydapt per modified Valent criteria.

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- Warnings and precautions of Rydapt include embryo-fetal toxicity and pulmonary toxicity.

- The most common adverse reactions (≥ 20%) with Rydapt use for the treatment of AML were febrile neutropenia, nausea, mucositis, vomiting, headache, petechiae, musculoskeletal pain, epistaxis, device-related infection, hyperglycemia, and upper respiratory tract infection.

- The most common adverse reactions (≥ 20%) with Rydapt use for the treatment of ASM, SM-AHN or MCL were nausea, vomiting, diarrhea, edema, musculoskeletal pain, abdominal pain, fatigue, upper respiratory tract infection, constipation, pyrexia, headache, and dyspnea.

- The recommended starting dose of Rydapt in AML is 50 mg orally twice daily with food on days 8 to 21 of each cycle of induction with cytarabine and daunorubicin, and on days 8 to 21 of each cycle of consolidation with high-dose cytarabine.

  The recommended starting dose of Rydapt in ASM, SM-AHN and MCL is 100 mg orally twice daily with food. Treatment should be continued until disease progression or unacceptable toxicity. Refer to the drug label for dose modifications.

- Prophylactic anti-emetics should be administered before Rydapt treatment to reduce the risk of nausea and vomiting. QT interval assessments may be considered if patients are concurrently taking medications that may prolong the QT interval.

- The wholesale acquisition cost of Rydapt is $7,495 for a 14-day package and $14,990 for a 28-day package.

- Novartis plans to launch Rydapt as 25 mg capsules in the first week of May.

- ncluding codeine, to treat cough in children.